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(54) Title: L-2',3'-DIDEOXY NUCLEOSIDE ANALOGS AS ANTI-HEPATITIS B (HBV) AND ANTI-HIV AGENTS

(57) Abstract

The present invention relates to the discovery that certain dideoxynucleoside analogs which contain a dideoxy ribofuranosyl moiety having an L-configuration (as opposed to the naturally occurring D-configuration) exhibit unexpected activity against Hepatitis B virus (HBV). In particular, the compounds according to the present invention show potent inhibition of the replication of the virus in combination with very low toxicity to the host cells (i.e., animal or human tissue). Compounds according to the present invention exhibit primary utility as agents for inhibiting the growth or replication of HBV, HIV and other retroviruses, most preferably HBV. The compound 1-(2,3-dideoxy-beta-L-ribofuranosyl)-5-fluorocytosine is shown to be a potent anti-HIV agent with low toxicity to host cells.

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L-2',3'-Dideoxy Nucleoside Analogs As Anti-Hepatitis B (HBV) and Anti-HIV Agents

Field of the Invention

This invention relates to dideoxy nucleoside analogs. These compounds exhibit significant activity against retroviruses, and in particular, Hepatitis B virus. This invention also relates to pharmaceutical compositions containing these compounds and to methods of inhibiting the growth or replication of Hepatitis B virus as well as treating Hepatitis B viral infections in animals and in particular, humans.

Background of the Invention

Hepatitis B virus (HBV) infection is a major health problem throughout the world. HBV is a causative agent of both an acute and chronic form of hepatitis. It is estimated that more than 200 million people worldwide are chronic carriers of HBV.

HBV belongs to the family Hepadnaviridae, which includes a number of related viruses which primarily infect small rodents. All members of the hepadnavirus family have a number of characteristics in common such as morphological appearance, antigenic makeup and DNA size and structure. Pathological findings following infection with the members of this family are quite similar. Studies show that the replication and spread of the viruses of this family are dependent upon the reverse transcriptase of an RNA intermediate.

HBV itself is a double-stranded DNA virus. Its DNA polymerase catalyzes both DNA-dependent and RNA-dependent RNA synthesis. The life cycle of HBV involves the enzyme reverse transcriptase in its DNA replication. There is presently no effective drug for the treatment of an HBV infection.

The best defense against Hepatitis B viral infection is vaccination. However, even with the advent of immunization programs, the disease remains a severe worldwide problem. Although acute Hepatitis B viral infections are generally self-limiting, in many instances the disease can progress to the chronic state. A Hepatitis B viral infection also creates a risk to fulminant hepatitis. In addition, Hepatitis B viral infections are closely associated with hepatocellular carcinoma.

Present therapy for the treatment of chronic Hepatitis B viral infections includes the administration of interferon alpha, and various nucleoside analogs such as adenine arabinoside or its monophosphate (ara-AMP). These therapeutic approach s have met with limited success. [illegible] of AZT, acyclovir and f scarnet

(in the case f fulminant hepatitis) to treat hepatitis has also been tried with little, if any, success.

Several 2',3'-dideoxynucleoside analogs have been reported in th literature to exhibit potent activity against Hepatitis B virus in culture. In particular, the nucleoside analogs (+) and (-)-2',3'-Dideoxy-3'-thiacytidine ((±) SddC) have shown to be potent inhibitors of Hepatitis B virus and the (-)isomer was particularly interesting in that it exhibited relatively low toxicity along with its potent activity. The 5-fluoro analog ((±)5-FSddC) was also shown to exhibit potent activity. (Chang, et al., Jour. Biol. Chem., 267, 222414, 1992 and Chang, et al., Jour. Biol. Chem., 267, 13938, 1992).

Another viral disease which recently has been studied greatly and treated with only limited success is AIDS. AIDS is a generally fatal disease caused by a human pathogenic retrovirus known as human T-lymphotropic virus type III (HTLV III), lymphadenopathy-associated virus (LAV) or human immunodeficiency virus (HIV).

In comparison with the other T-lymphotropic retroviruses HTLV I and II, HTLV III (HIV) and lymphoadenopathy viruses are nontransforming cytopathic viruses without immortalizing activity. The viral replication process is believed to be an important event in the progress of AIDS. It is further believed that the enzyme reverse transcriptase plays an essential role in the elaboration and life cycle of HIV and consequently, the progress of the disease. It is therefore believed that this enzyme may be a particularly appropriate target for the development of potential drugs against AIDs because of the absence of such an enzyme in the uninfected host cell. Recently, investigators have studied a number of anti-viral agents as potential anti-AIDS agents, including ribavirin and suramin, among others.

A number of nucleosides have played important roles in the treatment of HIV infections. 3'-azido-3'deoxythymidine (AZT) is a prime example, although recent reports raise some doubts about its effectiveness. A number of 2',3'-dideoxynucleoside analogs also have exhibited significant activity against human immunodeficiency virus (HIV), including 3'-deoxy-2',3'-didehydrothymidine (D4T), carbocyclic analog of 2',3'-dideoxy-2',3'-didehydroguanosin (Carbovir), 2',3'-did oxycytidine (DDC), 3'-azid -2',3'-dideoxyguanosin (AZG), 2',3'-dideoxyinosine (DDI), 2',3'-did oxy-2',3'-didehydrocytidine (D4C), 3'-fluoro-2',3'-dideoxyadenosine, 3'-fluoro-3'-deoxythymidine and 3'-azido-2',3'-did oxyuri[illegible], Larder, et al., Antimicrob. Agents

Chemother., 34, 436 (1990). Certain of these analogs, including ddC, are currently used as anti-HIV agents. Among the dideoxynucleosides, ddC has been shown to be among the most potent inhibitors of HIV.

Although research has concentrated on discovering an effective treatment protocol against HBV and HIV and certain potent anti-HBV and anti-HIV nucleoside analogs have been synthesized and characterized, an ideal drug has not been found.

The major problem in optimizing a treatment protocol against retroviral infections, including HBV and HIV, is to provide acceptable anti-viral activity while minimizing the toxicity to the host cell as well as the anti-mitochondrial DNA effects that many present anti-viral nucleosides exhibit.

The present invention relates to synthetic nucleosides which exhibit potent anti-viral activity (in particular, anti-HBV and anti-HIV activity) with significantly reduced toxicity to the host cell. In contrast to the prior art compounds, the analogs of the present invention represent a viable medicinal therapeutic approach to HBV infections and an improved approach to the inhibition of HIV and the treatment of AIDS.

Brief Description of the Invention

The present invention relates to the surprising discovery that certain dideoxynucleoside analogs which contain a dideoxy ribofuranosyl moiety having an L-configuration (as opposed to the naturally occurring D- configuration) exhibit unexpected activity against Hepatitis B virus (HBV). In particular, the compounds according to the present invention show potent inhibition of the replication of the virus in combination with very low toxicity to the host cells (i.e., animal or human tissue). This is an unexpected result.

Compounds according to the present invention exhibit primary utility as agents for inhibiting the growth or replication of HBV, HIV and other retroviruses, most preferably HBV. Certain of these agents also may be useful for inhibiting the growth or replication of other viruses or for treating other viral infections, certain types of fungal infections, microbial infections and/or related disease states. In addition, certain of these agents may be useful as intermediates for producing or synthesizing related chemical species.

Compounds of the present invention find particular use in combating viral infections which afflict animals, and in particu-

lar, humans suffering fr m hepatitis B viral infections. Compounds acc rding to the present inventi n offer great potential as therap utic agents against a disease state (chronic HBV infection) for which there pr sently are few real therapeutic options. The compounds according to the present invention may b used alone or in combination with agents or other therapeutic treatments.

The compounds of the present invention are dideoxynucleoside analogs which contain a dideoxyribofuranosyl moiety having an L-configuration (in contrast to the natural D-configuration of the sugar moiety). Compounds according to the present invention are disclosed which contain natural or synthetic nucleic acid bases including adenine, guanine, cytosine, thymine and uracil and substituted derivatives of th se bases. Compounds of the present invention may also contain certain modifications of the ribofuranosyl moiety.

The present invention also relates to methods for inhibiting the growth or replication of HBV comprising exposing the virus to an inhibitory effective amount or concentration of at least one of the disclosed L-2',3'-dideoxynucleoside analogs. This method may be used in comparison tests such as assays for determining the activities of related anti-HBV compounds as well for determining the susceptibility of a patient's HBV infection to one of the compounds according to the present invention. The present invention may also be used in treating viral infections.

The present invention also relates to a method for inhibiting the growth or replication of HIV comprising exposing the virus to an inhibitory effective amount or concentration of 1-(2,3-dideoxy-beta-L-ribofuranosyl)-5-fluorocytosine. This method may be used in comparison tests such as assays for determining the activities of related anti-HIV compounds as well for determining the susceptibility of a patient's HIV infection to the compound. The present invention may also be used in treating viral infections.

The therapeutic aspect according to the present inventi n relates to methods for treating retroviral infections in animal or human patients, in particular, HBV or HIV infections in humans comprising administering anti-viral effective amounts of the compounds according to the present inv nti n to inhibit the growth or replication f the viruses in th animal or human pati nt being treated.

Pharmaceutical compositions based upon these novel chemical compounds comprise the abov -describ d compo[illegible] in a

therapeutically effective amount for treating a viral, preferably a H patitis B viral, and in certain instances, a HIV infection, optionally in combination with a pharmaceutically acceptable additiv , carrier or xcipient.

Certain of the compounds, in pharmaceutical dosag form, may be used as prophylactic agents for inhibiting the growth or replication of the viral infection. These may be particularly appropriate as anti-HBV or anti-HIV agents. In certain pharmaceutical dosage forms, the pro-drug form of the compounds according to the present invention are preferred.

While not being limited by way of theory, it is beli ved that the compounds according to the present invention induce their inhibitory effect on the growth or replication of HBV or HIV by functioning as anti-metabolites of the reverse transcriptase enzyme of HBV and HIV.

The compounds according to the present invention are produced by synthetic methods which are readily known to those of ordinary skill in the art and include various chemical synthetic methods.

Brief Description of the Figures

Figures 1-11 (Schemes 1-11) depict the synthetic chemical steps which are used to synthesize the compounds according to the present invention. Schemes pertaining to the synthesis of a particular composition are referenced in the examples set forth herein.

Detailed Description of the Present Invention

The following definitions will be used throughout the specification to describe the present invention.

The term "dideoxy" is used throughout the specification to describe ribofuranosyl moieties which contain hydrogens rather than hydroxyls at the 2′ and 3′ positions of the sugar in the present compounds.

The term "didehydro" is used throughout the specification to describe ribofuranosyl moieties which contain a double b nd. For example, 2′,3′-didehydro refers to a ribofuran syl moi ty containing a double bond between the 2′ and 3′ carbons of the sugar.

Th term "inhibitory effective concentration" or "inhibitory eff ctiv amount" [illegible] throughout the specifica-

tion to describe concentrations or amounts of compounds according to the present invention which substantially or appreciably inhibit the growth or replication of susceptible viruses, especially including HBV or HIV.

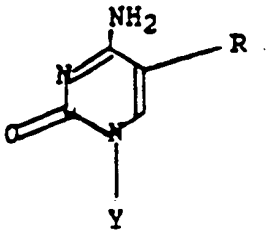
The term "therapeutic effective amount" is used throughout the specification to describe concentrations or amounts of compounds according to the present invention which are therapeutically effective in treating retroviral infections, and in particular, HBV or HIV infections in humans.

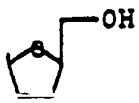
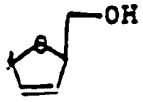
The term "L-configuration" is used throughout the specification to describe the chemical configuration of the dideoxyribofuranosyl moiety of compounds according to the present invention. The L-configuration of the sugar moiety of compounds of the present invention contrasts with the D-configuration of ribose sugar moieties of the naturally occurring nucleosides cytidine, adenosine, thymidine, guanosine and uridine.

The present invention relates to the surprising discovery that certain dideoxynucleoside analogs which contain a dideoxy ribofuranosyl moiety having an L-configuration (as opposed to the naturally occurring D- configuration) exhibit unexpected activity against Hepatitis B virus (HBV). In particular, the compounds according to the present invention show potent inhibition of the replication of the virus in combination with very low toxicity to the host cells (i.e., animal or human tissue).

The present invention also relates to the unexpected discovery that the compound 1-(2,3-dideoxy-beta-L-ribofuranosyl)-5-fluorocytosine (ß-L-FddC) is an extremely effective anti-HIV agent exhibiting relatively low toxicity, especially compared to 1-(2,3-dideoxy-beta-D-ribofuranosyl)cytosine (dideoxycytidine or ddC) which is presently used as one of the most effective anti-HIV compounds presently available. That ß-L-FddC would exhibit such exception anti-HIV activity and relatively limited toxicity to the host is an unexpected result, especially when compared to the anti-HIV activity of similar compounds.

The present invention relates to a first group of compounds according to the structure:

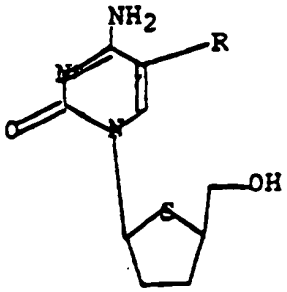


where Y is  or 

and R is F, Cl, Br, I or CH_3.

In this first group of compounds, R is preferably H or F.

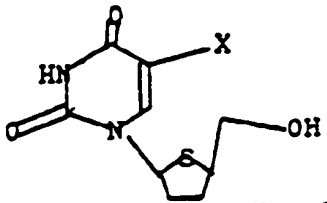
The present invention also relates to a second group of compounds according to the structure:

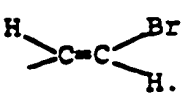


where R is H, F, Cl, Br, I or CH_3.

In this second group of compounds, R is preferably H or F, most preferably H.

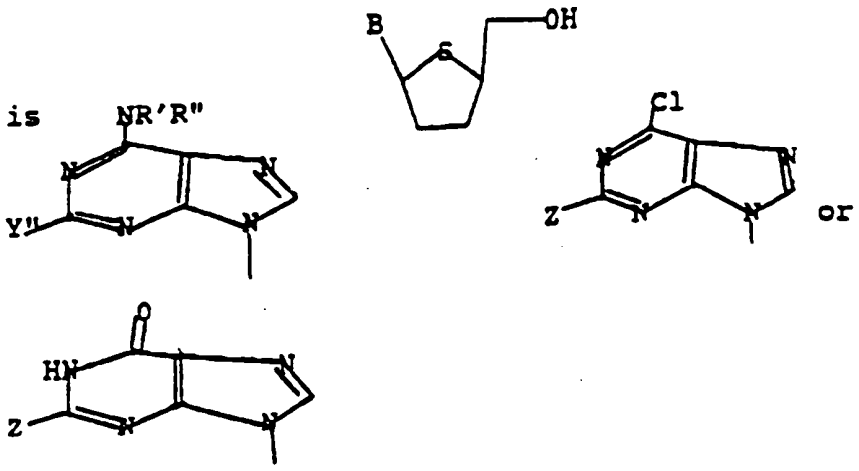
The present invention also relates to a third group of compounds according to the structure:



where X is H, F, Cl, Br, I, CH_3, $-C\equiv CH$, $-HC=CH_2$ or 

In this third group of compounds, X is preferably H, F or CH_3, most preferably CH_3.

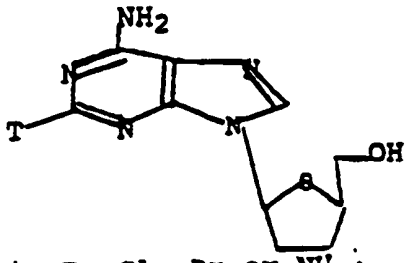
The present invention also relates to a fourth group of compounds according to the structure:



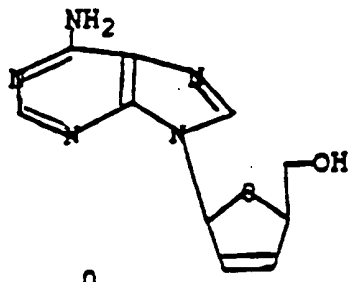
R' is H or CH_3;
R" is H or CH_3;
Y" is H, F, Br, Cl or NH_2 when R' and R" are H and
Y" is H when at least one of R'or R" is CH_3;
and Z is H or NH_2.

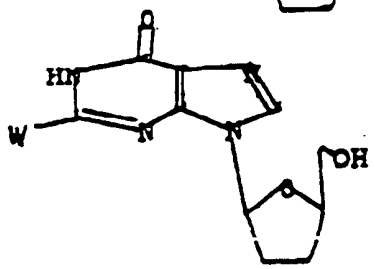
In this fourth group of compounds according to the present invention, R' and R" are preferably H and Y" is preferably H or R, most preferably H. Z is preferably NH_2.

The present invention also relates to compounds having the structures:

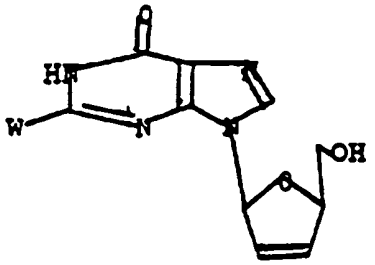


where T is F, Cl, Br or NH_2;



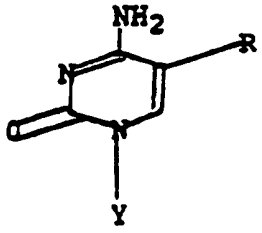


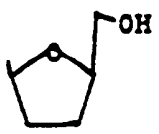
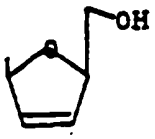
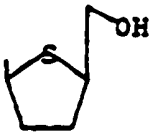
and



where W is H or NH_2.

In a first method aspect, the present invention relat s to a method for inhibiting the growth or replication of Hepatitis B virus comprising exposing the virus to an inhibitory effective concentration of a compound according to the structure:

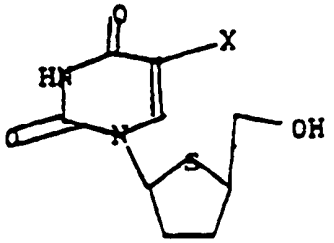


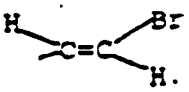
where Y is   or 

and R is H, F, Cl, Br, I or CH_3.

In this first method aspect, R is preferably H or F.

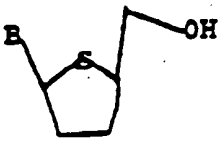
A sec nd meth d asp ct f r inhibiting the growth or replication of Hepatitis B virus according to the present invention comprises exposing th virus to an inhibitory effective concentration f a compound according to the structure:

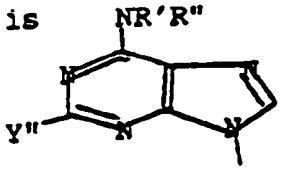


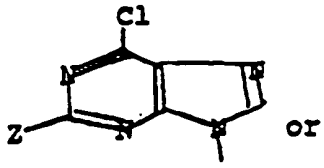
where X is H, F, Cl, Br, I, CH_3, $-C\equiv CH$, $-HC=CH_2$ or 

In this second method aspect, X is H, F or CH_3, most preferably CH_3.

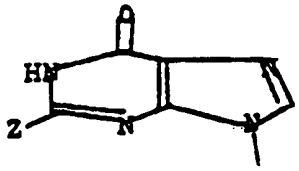
A third method aspect for inhibiting the growth or replication of Hepatitis B virus according to the present invention comprises exposing the virus to an inhibitory effective concentration of a compound according to the structure:



where B is 



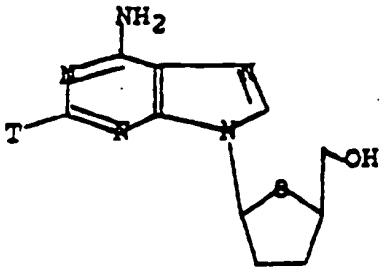
or



R′ is H or CH_3;
R" is H or CH_3;
Y" is H, F, Cl, Br or NH_2 when R′ and R" are H and
Y" is H when at least one of R′or R" is CH_3;
and Z is H or NH_2.

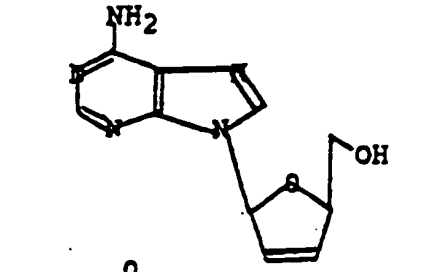
In this third method aspect of the present invention, R′ and R" are preferably H and Z is preferably NH_2.

A fourth method aspect for inhibiting the growth or replication of Hepatitis B virus according to the present invention comprises exposing the virus to an inhibitory concentration of a compound according to the structur :

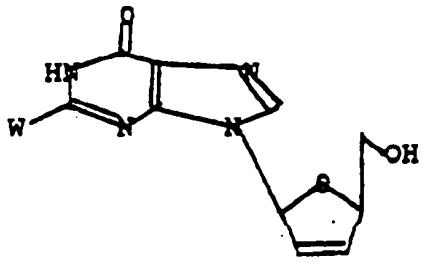


where T is H, F, Cl, Br or NH_2.
In this fourth method T is preferably H or F, most preferably H.

A fifth method aspect for inhibiting the growth or replication of Hepatitis B virus according to the present invention comprises exposing the virus to an inhibitory concentration of a compound according to the structure:

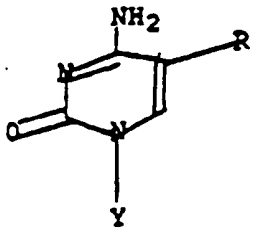


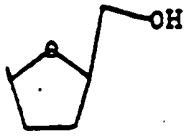
or



where W is H or NH_2.

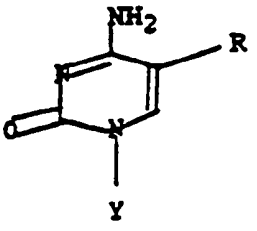
A sixth method aspect according to the present invention relates to the inhibition f the growth or replication f human immunodeficiency virus according to the present invention comprising exposing the virus to an inhibitory concentration of a compound according to the structure:

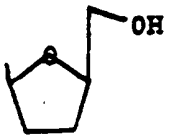


where Y is 

and R is F.

The present invention is also directed to a method for treating a patient suffering from an infection caused by the human immunodeficiency virus comprising administering to said patient a therepeutically effective concentration of a compound according to the structure:



where Y is 

and R is F.

The compounds according to the present invention are primarily useful for their anti-retroviral activity and in particular, their anti-HBV or anti-HIV activity. The present compounds may also be useful for their biological activity as antifungal or antimicrobial agents. In addition, these compositions may also find use as interm diates in the chemical synthesis of other nucleoside or nucleotide analogs which are, in turn, useful as therap utic agents or for other purposes. Preferably these compositions find use as novel anti-HBV agents and, in addition, in the case of β-L-FddC, also as a novel anti-

HIV agent.

In general, the most preferred anti-viral, especially anti-HBV r anti-HIV compounds, according to the present invention includ thos which are less cytotoxic to the host cells and more active to the targeted virus. Certain of the compounds, in pharmaceutical dosage form, may be used as prophylactic agents. These may be particularly appropriate as antiviral agents, and in particular, anti-HBV or anti-HIV agents. Because of its very low toxicity to the patient, β-L-FddC is an especially effective anti-propylactic compound for inhibiting HIV and preventing AIDS.

The compounds according to the present invention are produced by synthetic methods which are readily known to those of ordinary skill in the art and include various chemical synthetic methods as elaborated in significantly more detail in the Examples which follow. In general, compounds according to the present invention are synthesized by condensing a previously synthesized nucleoside base onto the appropriate sugar synthon which will ultimately give rise to a nucleoside analog having the desired dideoxyribofuranosyl moiety of L-configuration. In certain instances, the synthetic pathway may deviate from the general synthetic pathway for a specific nucleoside analog (for example, in the case of 1-(2,3-dideoxy-beta-L-ribofuranosyl)cytosine and 1-(2,3-dideoxy-beta-L-ribofuranosyl)uracil as set forth in Example 1 and Scheme 3.

During chemical synthesis of the various compositions according to the present invention, one of ordinary skill in th art will be able to practice the present invention without undu experimentation. In particular, one of ordinary skill in the art will recognize the various steps that should be performed to introduce a particular substituent at the desired position of the base or a substituent at the desired position on the sugar moiety. In addition, chemical steps which are taken to "protect" functional groups such as hydroxyl or amino groups, among others, as well as "de-protect" these same functional groups, will be recognized as appropriate within the circumstances of the syntheses.

The therapeutic aspect according to the present invention relates to methods for treating retroviral infections in animal or human patients, in particular, HBV or HIV infections in humans comprising administering anti-viral effective amounts of th compounds according to th present invention to inhibit the growth or replicati n of the viruses in the animal or human pati nt being treated.

Pharmaceutical compositions based upon these novel chemical compounds comprise the above-described compounds in a therapeutically effective amount for treating a viral, preferably a Hepatitis B viral or HIV infection, optionally in combination with a pharmaceutically acceptable additive, carrier or excipient. One of ordinary skill in the art will recognize that a therapeutically effective amount will vary with the infection or condition to be treated, its severity, the treatment regimen to be employed, the pharmacokinetics of the agent used, as well as the patient (animal or human) treated.

In the pharmaceutical aspect according to the present invention, the compound according to the present invention is formulated preferably in admixture with a pharmaceutically acceptable carrier. In general, it is preferable to administer the pharmaceutical composition in orally-administrable form, but certain formulations may be administered via a parenteral, intravenous, intramuscular, transdermal, buccal, subcutaneous, suppository or other route. Intravenous and intramuscular formulations are preferably administered in sterile saline. Of course, one of ordinary skill in the art may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration without rendering the compositions of the present invention unstable or compromising their therapeutic activity. In particular, the modification of the present compounds to render them more soluble in water or other vehicle, for example, may be easily accomplished by minor modifications (salt formulation, esterification, etc.) which are well within the ordinary skill in the art. It is also well within the routineer's skill to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in patients.

In certain pharmaceutical dosage forms, the pro-drug form of the compounds, especially including acylated (acetylated or other) derivatives, pyridine esters and various salt forms of the present compounds are preferred. One of ordinary skill in the art will recognize how to readily modify the present compounds to pro-drug forms to facilitate delivery of active compounds to a targeted site within the host organism or patient. The routineer also will take advantage of favorable pharmacokinetic parameters of the pro-drug forms, where applicable, in delivering the present compounds to a target d[illegible]thin the host organism or patient to maximize the intended effect of the compound.

The amount of compound included within therapeutically active formulations according to the present invention is an effective amount for treating the infection or condition, in its most preferred embodiment, an HBV infection, or in the case of ß-L-FddC, an HIV infection. In general, a therapeutically effective amount of the present compound in dosage form usually ranges from slightly less than about 1 mg./kg. to about 25 mg./kg. of the patient or considerably more, depending upon the compound used, the condition or infection treated and the route of administration. In the case of HBV infections, the compound is preferably administered in amounts ranging from about 1 mg/kg to about 25 mg/kg. In the case of the use of ß-L-FddC as an anti-HIV agent, the compound is preferably administered in an amount ranging from about 1 mg/kg to about 25 mg/kg, depending upon the pharmacokinetics of the agent in the patient. This dosage range generally produces effective blood level concentrations of active compound ranging from about 0.04 to about 100 micrograms/cc of blood in the patient.

Administration of the active compound may range from continuous (intravenous drip) to several oral administrations per day (for example, Q.I.D.) and may include oral, topical, parenteral, intramuscular, intravenous, sub-cutaneous, transdermal (which may include a penetration enhancement agent), buccal and suppository administration, among other routes of administration.

To prepare the pharmaceutical compositions according to the present invention, a therapeutically effective amount of one or more of the compounds according to the present invention is preferably intimately admixed with a pharmaceutically acceptabl carrier according to conventional pharmaceutical compounding techniques to produce a dose. A carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral. In preparing pharmaceutical compositions in oral dosage form, any of the usual pharmaceutical media may be used. Thus, for liquid oral preparations such as suspensions, elixirs and solutions, suitable carriers and additives including water, glycols, oils, alcohols, flavouring agents, preservatives, colouring agents and the like may be used. For solid oral preparations such as powders, tablets, capsules, and for solid preparations such as suppositories, suitable carriers and additives including starches, sugar carriers, such as dextrose, mannitol, lactose and related carriers, diluents, granulating agents, lubricants, binders, disintegrating agents

and the like may be used. If desired, the tablets or capsules may be enteric-coated or sustained release by standard techniques.

For parenteral formulations, the carri r will usually comprise sterile water or aqueous sodium chloride solution, though other ingredi nts, including those which aid dispersion, also may be included. Of course, where sterile water is to be used and maintained as sterile, the compositions and carriers must also be sterilized. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed.

In particularly preferred embodiments according to th present invention, the compounds and compositions are used to treat retroviral infections of mammals and in particular humans. In its most preferred embodiment, the compounds are used to tr at HBV infections, including chronic HBV infection. The comound ß-L-FddC is effectively used to treat HIV infections, including AIDS. Generally, to treat HBV or HIV infections, the compositions preferably will be administered in oral dosage form in amounts ranging from about 250 micrograms up to about 500 mg. or more up to four times a day. The present compounds are preferably administered orally, but may be administered parenterally, topically or in suppository form.

The compounds according to the present invention, because of their unexpectedly low toxicity to host cells, may advantageously be employed prophylactically to prevent infection or to prevent the occurrence of clinical symptoms associated with the viral infection. Thus, the present invention also encompasses methods for the therapeutic or prophylactic treatment of viral infections, and in particular HBV or HIV infections. This prophylactic method comprises administering to a patient in need of such treatment an amount of a compound according to the present invention effective for alleviating, and/or preventing the viral infection. In the prophylactic treatment according to the present invention, it is preferred that the antiviral compound utilized should be as low in toxicity and preferably non-toxic to the patient. It is particularly preferred in this aspect of the present invention that the compound which is used should be maximally effective against the virus and should exhibit a minimum of toxicity to the patient. In th cas of ß-L-FddC, this compound may be administered within the same dosage range for therapeutic treatment (i.e., about 250 micrograms up to about 500 mg. fr m ne t four times per day for an ral dosage

form) as a prophylactic agent to prevent the rapid proliferation of HIV or alternatively, to prolong the onset of AIDS in a patient.

In addition, compounds according to the present invention may be administered alone or in combination with other agents, especially including other compounds of the present invention. Certain compounds according to the present invention may be effective for enhancing the biological activity of certain agents according to the present invention by reducing the metabolism or inactivation of other compounds and as such, are co-administered for this intended effect. In the case of ß-L-FddC, this compound may be effectively combined with any one or more of the standard anti-HIV agents which are presently utilized including AZT, DDC, and DDI, among others.

In a particularly preferred pharmaceutical composition and method for treating HBV infections, an inhibitory effective amount of 1-(2,3-dideoxy-beta-L-ribofuranosyl)cytosine and/or 1-(2,3-dideoxy-beta-L-ribofuranosyl)5-fluoro-cytosine is administered to a patient suffering from an HBV infection to alleviate the symptoms of such infection.

In a particularly preferred pharmaceutical composition and method for treating HIV infections, an inhibitory effective amount of 1-(2,3-dideoxy-beta-L-ribofuranosyl)5-fluorocytosine is administered to a patient suffering from an HIV infection and/or AIDS to alleviate the symptoms of such infection.

While not being limited by way of theory, it is believed that the compounds according to the present invention primarily induce their inhibitory effect on the growth or replication of HBV or HIV by functioning as anti-metabolites of the reverse transcriptase enzyme of the virus.

The present invention is now described, purely by way of illustration, in the following examples. It will be understood by one of ordinary skill in the art that these examples are in no way limiting and that variations of detail can be made without departing from the spirit and scope of the present invention.

EXAMPLES

I. Chemical Synth sis of L-2'3'-dideoxynucleoside Analogs

Examples 1-9

In general, compounds of the present invention are synthesized according to the chemical synthetic method described hereinbelow. The synthetic chemical methodology employed to synthesize the present compounds represents modifications of literature procedures. The references from which a related chemical reaction have been modified to produce the present compounds are set forth in the examples, below.

Melting points were determined using a MelTemp apparatus and are uncorrected. Proton NMR spectra were recorded on a Varian EM390 or Bruker WM 250 instrument and reported as ppm (delta) downfield from $(CH_3)_4Si$. Ultraviolet spectra were recorded on a Beckman 25 spectrophotometer. Analytical thin-layer chromotography (TLC) was done using Merck EM Silica Gel 60 F_{254} precoated sheets. Column chromatography employed Merck EM silica gel using standard organic solvents (CH_2Cl_2/MeOH or CH_2Cl_2/EtOAC varying in volume/volume ratio) unless otherwise indicated primarily to separate the alpha and beta anomeric mixtures.

EXAMPLE 1

Synthesis of 1-(2,3-Dideozy-beta-L-ribofuranosyl)cytosine, 1-(2,3-Dideoxy-beta-L-ribofuranosyl)-5-fluoro-, -5-bromo-, -5-chloro-, -5-iodo- and -5-methylcytosine

The methodology of Taniguchi et al. (Tetrahedron, 30, 3532, 1974) and Farina et al. (Tetrahedron Lett., 29, 1239, 1988) for the syntheses of D-ribose derivatives provided a model for our synthetic approach to the syntheses of the corresponding L-ribose derivatives. Nitrous acid deamination of D-glutamic acid (1) gave lactone 2, which was then converted to the corresponding ester 3 by treatment of compound 2, with ethanol and catalytic amount of p-toluenesulfonic acid (See Scheme 1). Reduction of compound 3 with $NaBH_4$ in ethanol gave (R)-4-(hydroxymethyl)-4-butyrolactone (4). Protection of the hydroxy group of compound 4 with tert-butyldimethylsilyl chloride in methylene chloride using imidazole as catalyst produced (R)-4-[[(tert-butyldimethylsilyl)oxy]methyl)-4-butyrolactone (5), which was then conv rt d to the corresponding lactol 6 by reduction with diisobutyaluminum hydride (DIBAL) in t luene at -78°C. Acetylation of 6 with acetic anhydride and tri thylamin afforded the

k y sugar intermediat , 1-O-acetyl-5-O-(tert-butyldimethylsilyl)-2,3-dideoxy-L-ribofuranose (7) as a mixture of alpha and beta anomers: MS, m/e 231 (M^+-CH_3CO), 215 (M^+-CH_3COO); NMR($CDCl_3$)) delta 0.10 (s, 6H, $SiMe_2$), 0.95 (s, 9H, tert-butyl), 1.85-2.15 (m, 7H, CH_2CH_2 and $COCH_3$), 3.50-3.65 (M, 2H, 5-H), 4.10-4.30 (m, 1H, 4-H), 6.20-6.30 (m, 1H, 1-H).

Uracil, 5-fluoro, 5-bromo-, 5-chloro- and 5-iodouracil as well as thymine were coupled with acetate 7 by the methodology of Okabe et al. (J. Org. Chem., 53, 4780, 1988) with minor modifications.

Silylated 5-fluorouracil, prepared from 5-fluorouracil, (4.3g, 33 mmol) was reacted with acetate 7 (8.3g, 30 mmol) and ethylaluminum dichloride (16.7 mL of a 1.8 M solution in toluene, 30 mmol) in methylene chloride at room temperature for 3 hrs. to give 8.5 g (83%) of 1-(5-O(tert-butyldimethylsilyl)-2,3-dideoxy-alpha, beta,-L-ribofuranosyl)-5-fluorouracil (8,R = F) as a 2:3 alpha/beta anomeric mixture. The alpha and beta anomers were separated by silica gel chromatography. The beta anomer (9): NMR ($CDCl_3$) delta 0.10 (s, 6H, $SiMe_2$), 0.95 (s, 9H, tert-butyl), 1.80-2.45 (m, 4H, 2'-H and 3'-H), 3.50-3.70 (m, 1H, 4'-H), 3.95-4.15 (m, 2H, 5'-H), 5.90-6.05 (m, 1H, 1'-H), 8.10-8.20 (d, 1H, 6-H), 9.30-9.50 (br, 1H, NH, D_2O exchangeable); the alpha isomer: NMR ($CDCl_3$) delta 0.10 (s, 6H, $SiMe_2$), 0.95 (s, 9H, tert-butyl), 1.90-2.55 (m, 4H, 2'-H and 3'-H), 3.60-3.65 (m, 2H, 5'-H), 4.30-4.50 (m, 1H, 4'-H), 5.90-6.05 (m, 1H, 1'-H), 7.30-7.40 (d, 1H, 6-H), 9.00-9.30 (br, 1H, NH, D_2O exchangeable). Treatment of th beta anomer (9, 3g, 8.7 mmol) with 4-chlorophenyl phosphorodichloridate (6.2 mL, 37.8 mmol) and 1,2,4-triazole (7.9g , 114 mmol) in anhydrous pyridine (60mL) at room temperature yielded the 4-triazolylpyrimidinone derivative 10. The crude product 10 was treated with a mixture of ammonium hydroxide/dioxane (1.:3, v/v) to afford the 2',3'-dideoxycytidine drivative 11 (1.2 g, 40%), which was then deblocked by reacti n with tetra-n-butylammonium fluoride in THF at room temperature for 20 min to afford the target compound 1-(2,3-dideoxy-beta-L-ribofuranosyl)-5-fluorocytosine (12, R =F, L-FDDC): mp 147-149°C; NMR (DMSO-d_6) delta 1.85-2.35 (m, 4H, 2'-H and 3'-H), 3.60-3.82 (m, 2H, 5'-H), 4.25 (m, 1H, 4'-H), 5.15 (t, 1H, 5'-OH, D_2O exchangeable), 5.95-6.15 (m, 1H, 1'-H), 7.45 (br s, 2H, 4-NH_2, D_2O exchangeable), 8.22 (d, 1H, 6-H).

To synthesize 1-(2,3-dideoxy-beta-L-ribofuranosyl)cytosine, 1(2,3-dideoxy-b ta-L-ribofuranosyl)-5-bromo-, -5-chloro-, -5-iodo-, or -5-methylcyt sine, the analogous

proc dure used to synth siz th 5-fluoro derivative was employed. For the coupling reaction, the corresponding silylated 5-bromo-, -5-chloro-, -5-iodo-, or -5-methylcytosine was used instead of 5-fluorouracil. All other steps are analogous to those for th synthesis of the 5-fluoro derivatitv 12 (R = F).

Tr atm nt f compound 9 with tetra-n-butylammonium fluoride in THF gave the corresponding uracil derivative 13.

Compound 12 (R=H,F,Cl,I and CH_3) was also synthesized by an alternative methodology (See Scheme 2), by which the silylated compound 15 (R= H,F,Cl,I and CH_3), prepared from the corresponding cytosine (14, R=H) and its derivatives 14 (R= F,Cl,I and CH_3), were directly coupled with acetate 7, followed by separation of the alpha and beta anomers 16 and removal of the protecting group.

Compound 12 (R=H) was also synthesized by a stereospecific approach (See Scheme 3), in which the possibility of producing the alpha anomer was eliminated. O-2,2'-Anhydrouridine 19 was prepared by the method of Holy (Collection Czechoslov. Chem. Commun., 37, 4072, 1972) from L-arabinose (17) via the intermediate oxazoline derivative 18. Treatment of compound 19 with tert-butyldimethylsilyl chloride in pyridine gave the protected chloro derivative, 1-[5-O(-tert-butyldimethylsilyl)-2-chloro-2-deoxy-beta -L-ribofuranosyl]uracil (20, R=H). Conversion of compound 20 to the corresponding 2',3'-unsaturated nucleoside 22 was achieved by previously developed methodology (Lin et al., Tetrahedron Lett., 31, 3829, 1991). Treatment of compound 20 with phenyl chlorothionocarbonate and 4-dimethylaminopyridine in acetonitrile under nitrogen at room temperature yielded the 2'-chloro-3'-O-phenoxythiocarbonyl derivative 21, which has two different vicinal groups at the 2'- and 3'-positions. Reduction of compound 21 with tri-n-butyltin hydride and azobisisobutyronitrile (AIBN) in dry toluene at 60-70°C for 4h produced the 2',3'-unsaturated derivative 22 as a foam: NMR ($CDCl_3$) delta 0.10 (s, 6H, $SiMe_2$), 0.95 (s, 9H, tert-butyl), 3.90 (m, 2H, 5'-H), 4.90 (m, 1H, 4'-H), 5.65-5.75 (d, 1H, 5-H), 5.80-5.90 (d, 1H, 3'-H), 6.25-6.35 (d, 1H, 2'-H), 7.05-7.10 (m, 1H, 1'-H), 7.75-7.85 (d, 1H, 6H), 9.55 (s, 1H, -NH, D_2O exchangeable). Catalytic hydrogenation of compound 22, followed by treatment with 4-chlorophenyl phosphorodichloridate and 1,2,4-triazole yielded the 4-triazolylpyrimidinone derivative 24, which was then converted to the d sired 1-(2,3-dideoxy-beta-L-ribofuranosy)cytosin 12 (R=H, L-DDC) by treatment of 24 with NH_4OH/dioxan , foll wed by d blocking of the 5'- protecting group

as pr viously d scribed.

Comp und 12 (R=H, L-DDC): mp 194-196°C; ^{1}H NMR (DMSO-d_6) 1.74-2.24 (m, 4-H, 2'-H and 3'-H), 3.49-3.65 (m, 2H, 5'-H), 3.98-3.99 (m, 1H, 4'-H), 4.96-5.00 (t, 1H, 5'-OH, D2O exchangeable), 5.65-5.68 (d, 1 H, 5-H), 5.85-5.93 (m, 1H, 1'-H), 7.01-7.06 (m 2H, -NH2, D2O exchang able), 7.87-7.90 (d, 1H, 6-H).

Treatment of compound 23 with tetra-n-butylammonium fluoride in THF gave the corresponding uracil derivative 13 (R=H): ^{1}HNMR (DMSO-d_6) delta 1.80-2.05 (m, 4-H, 2'-H and 3'-H), 3.45-3.60 (m, 2H, 5'-H), 3.85-4.05 (m, 1H, 4'-H), 4.85-5.00 (t, 1H, 5'-OH, D_2O exchangeable), 5.45-5.55 (d, 1H, 5-H), 5.80-6.00 (m, 1H, 1'-H), 7.80-7.90 (d, 1H, 6-H), 11.10 (s, 1H, NH, D2O exchangeable).

EXAMPLE 2
2',3'-Dideoxy-, 2',3'-Dideoxy-N-methyl- and 2',3'-Dideoxy-N,N-dimethyl-beta-L-adenosine, and 2',3'-Dideoxy-L-inosine and 2',3'-Dideoxy-beta-L-guanosine

The synthesis of 2',3'-dideoxy-, 2'3'-dideoxy-6-N-methyl-, and 2',3'-dideoxy-N,N-dimethyl-beta-L-adenosine, and 2',3'-dideoxy-beta-L-inosine and 2',3'-dideoxy-beta-L-guanosine (See Scheme 4) was based on the methodology reported by Fujimori et al. (Nucleoside & Nucleotides, 11, 341, 1992) for the synthesis of purine 2'-deoxynucleosides. Treatment of 6-chloropurine with NaH (60% in oil, washed with n-hexane) and acetate 7 in anhydrous acetonitrile under argon produced 6-chloro-9-[(5-O-tert-butyldimethylsilyl)-2,3-dideoxy-beta-L-erythro-pentofuranosyl]purine (26) together with the corresponding N-7 glycosyl isomer, which was separated by silica gel chromatography. Subsequent treatment of compound 26 with NH_3/CH_3OH, CH_3NH_2/CH_3OH, or $(CH_3)_2NH/CH_3OH$ at elevated temperature, followed by deprotection with tetra-n-butylammonium fluoride in THF afforded 2',3'-dideoxy-L-adenosine (27, R=R'= H), 2',3'-dideoxy-N-methyl-beta-L-adenosine (27, R= H, R'= CH_3,) and 2'3'-dideoxy-N,N-dimethyl-beta-L-adenosine (27, R=R'=CH_3), respectively. Treatment of compound 26 with tetra-n-butylammonium fluoride in THF, followed by alkaline hydrolysis f the deblocking nucleoside (28) with 2 N KOH/dioxane (1:1, v/v) gave 2'3'-dideoxy-L-inosine (29). Similarly, treatment of 2-amino-6-chloropurine with NaH (60% in oil, washed with n-hexane) and acetate 7 in anhydrous acetonitrile under argon afforded 2-amino-6-chloro-9-[(5-O-tert-butyldimethylsilyl)-2,3-dideoxy-beta-L-erythro-pentofuranosyl]purine (30). Conversi n f comp und 30 t the final product, 2'3'-dideoxy-beta-L-guanosine (32) was

achieved via the int rmediate 31 by deblocking with tetra-n-butylammonium fluoride in THF nd alkaline hydrolysis with 2 N KOH/dioxane (1:1,v/v).

EXAMPLE 3
2-Chloro-, 2-Bromo-, 2-Amino-, and 2-Fluoro-2',3'-dideoxy-beta-L-adenosine

These compounds are synthesized as described in Scheme 5 by the methodology employed in Example 2. 2,6-dichloropurine, prepred by the method described by Elion and Hitching (J. Am. Chem. Soc., 78, 3508, 1956) was treated with NaH (60% in oil, washed with n-hexane) and acetate 7 in anhydrous acetonitrile under argon to give 2,6-dichloro-9-[(5-O-tert-butyldimethylsilyl)-2,3-dideoxy-beta-L-erythro-pentofuranosyl]purine (33) and the corresponding N-7 glycosyl isomer, which was separated by silica gel chromatography. Treatment of compound 33 with NH_3/CH_3OH at elevated temperature, followed by deprotection with tetra-n-butylammonium fluoride in THF afforded 2-chloro-2',3'-dideoxy-L-adenosine (34). Treatment of dibromopurine with NaH (60% in oil, washed with n-hexane) and acetate 7 in anhydrous acetonitrile under argon to produce 6-bromo-9-[(5-O-tert-butyldimethylsilyl)-2,3-dideoxy-beta-L-erythro-pentofuranosyl]purine (31) together with the corresponding N-7 glycosyl isomer, which was separated by silica gel chromatography. Subsequent treatment of compound 31 with NH3/CH3OH at elevated temperature, followed by deprotection with tetra-n-butylammonium fluoride in THF afforded 6-bromo-(2,3-dideoxy-beta-L-erthro-pentofuranosyl)purine (41). 2,6-Bis(benzamido)purine, prepared by the method described by Davoll and Lowy (J. Am. Chem. Soc., 73, 1650, 1951) was treated with NaH (60% in oil, washed with n-hexane) and acetate 7 in anydrous acetonitrile under argon produced 2,6-bis(benzamido)-9-[(5-O-tert-butyldimethylsilyl)-2,3-dideoxy-beta-L-erythro-pentofuranosyl]purine (37), which was then subsequently deblocked by reaction with tetra-n-butylammonium fluoride in THF and sodium ethoxide in ethanol to give 2-amino-2',3'-dideoxy-beta-L-adenosine (38). Treatment of compound 38 with sodium nitrite and 48-50% fluoroboric acid below -10°C yielded 2-fluoro-2',3'-did oxy-beta-L-adenosine (39).

EXAMPLE 4

1-(2,3-Didehydro-did oxy-beta-L-ribuofuranosyl)cytosine, 1-(2,3-Didehydro-dide xy-beta-L-ribofuranosyl)-5-fluoro-, -5-bromo-, -5-chloro-, -5-iodo-, and -5-methylcytosine

These compounds were synth sized as s t forth in Scheme 6 by a methdology d veloped for th syntheses of the related D-isomers (Lin, et al., Biochem. Phamacol., 36, 311, 1987; Lin, et al., Organic Preparations and Procedures Intl., 22, 265, 1990). Treatment of 2'-deoxy-L-uridine (40,R=H), was prepared by the procedure of Holy (Collection Czechoslov. Chem. Commun., 37, 4072, 1972), with 2 equivalents of methanesulfonyl chloride in dry pyridine at -5-0°C gave the 3',5' di-O-mesyl derivative (41, R=H). Conversion of compound 41 (R=H) to 2'-deoxy-3',5'-epoxy-beta-L-uridine (43, R=H) via the intermediate anhydronucleoside 42 (R=H) by treatment with 1 N NaOH according the procedure of Horwitz et al. (J Org.Chem., 32, 817, 1967). Treatment of compound 43 (R=H) with 1,2,4-triazole and 4-chlorophenyl phosphorodichloridate in dry pyridine yielded the 4-triazolylpyrimidinone 44 (R=H), which was then reacted with NH_4OH/dioxane to give the cytidine derivative 45 (R=H). Treatment of compound 45 (R=H) with potassium t-butoxide in DMSO afforded the final product 1-(2,3-didehydro-2,3-dideoxy-beta-L-ribofuranosyl)cytosine (46, R=H): ^{1}HNMR (DMSO-d_6) delta 3.50 (m, 2H, 5'-H), 4.72 (m, 1H, 4'-H), 4.92 (br s, 1H, 5'-OH, D_2O exchangeable), 5.64 (d, 1H, 5-H), 5.83 (m, 1H, 3'-H), 6.30 (m, 1H, 2'-H), 6.85 (m, 1H, 1'-H), 7.09-7.15 (br d, 2H, 4-NH2, D_2O exchangeable), 7.64 (D, 1H, 6-H).

EXAMPLE 5

2',3'-Didehydro-2',3'-dideoxy-beta-L-adenosine

2',3'-Didehydro-2',3'-dideoxy-beta-L-adenosine (51) was synthesized as shown in Scheme 7 by the methodology of Barton et al. (Tetrahedron, 49,2793,1993) and Chu et al. (J.Org. Chem., 54, 2217, 1989) for the preparation of the D-isomer. Treatment of L-adenosine (47) with tert-butyldimethlsilyl chloride and imidazole in dry DMF with exclusion of moisture for 20h gave 5'-O-(tert-butyldimethylsilyl)-beta-L-adenosine (48), which was then reacted with CS_2, 5 N NaOH solution, and CH_3I in DMSO to afford the 2',3'-O-bis(dithiocarbonate) derivative 49. Deoxygenation of 49 with triethylsilane and benzoyl peroxide under argon, followed by deprot ction of the lefin derivative 50 with tetra-n-butylamm nium fluoride in THF afforded the final product 51.

Synthesis f th corresponding 2',3'-Did hydro-2',3'-dideoxy-beta-L-guanosine and 2',3'-Didehydro-2',3'-dideoxy-beta-

L-inosin analogs followed th sam procedure as above, starting from L-guanosine and L-inosin respectively.

EXAMPLE 6
1-(2,3-Dideoxy-4-thio-beta-L-rib furanosyl)cytosine, 1-(2,3-Dideoxy-4-thio-beta-L-ribofuranosyl)-5-fluoro-, -5-chlor -, -5-br mo-, -5-iod -, and -5-methylcytosine

The methodology of Secrist et al. (J. Med. Chem. 35, 533, 1922) for the synthesis of 2',3'-dideoxy-4'-thio-D-nucleosides provided a useful example for our synthetic approach to the synthesis of 1-2',3'-dideoxy-4'-thio-beta-L-nucleoside analogs (See Scheme 8).

D-glutamic acid (1) was treated with sodium nitrite in hydrochloric acid to produce (R)-1,4-butyrolactone-4-carboxylic acid (2). Compound 2 was then reduced by borane-dimethyl sulfide complex in THF to give the corresponding (R)-4-(hydroxymethyl)-4-butyrolactone (4), which was subsequently treated with tert-butyldiphenylsilyl chloride in methylene chloride using imidazole as a catalyst to afford (R)-5-O-tert-butyldiphenylsilyl-4-hydroxymethyl-1,4-butyrolactone (53). The protected lactone 53 was opened with sodium hydroxide in ethanol and then converted to the methyl ester of 5-[(tert-butyldiphenylsilyl)oxy]-4-(R)-hydroxypentanoic acid (54) by reaction with dimethyl sulfate in dimethyl sulfoxide. Commpound 54 was transformed into the methyl ester of 5-[(tert-butyldiphenylsilyl)oxy]-4-(S)-iodopentanoic acid (55) by treatment with triphenylphosphine, imidazole and iodine. Displacement of the iodo group in compound 55 by thioacetate in toluene occurred readily to give the methyl ester of 4-(R)-(acetylthio)-5-[(tert-butyldiphenylsilyl)oxy]pentanoic acid (56). Compound 56 was then treated with 2 equivalents of diisobutylaluminum hydride (DIBAL) in toluene to reductively deprotect the sulfur and reduce the methyl ester to an aldehyde, thereby producing the thiolactol via spontaneous cyclization. The thiolactol was acetylated with acetic anhydride in pyridine to give 1-O-acetyl-5-O-(tert-butyldiphenylsilyl)-2,3-dideoxy-4-thio-L-ribofuranose (57): ^{1}HNMR ($CDCl_3$) delta 7.67 (m, 4H, ArH), 7.40 (m, 6H, ArH), 6.10 (m, 1H, 1-H), 3.70 (m, 1H, 4-H), 3.52 (m, 2H, 5-H), 2.20 (m, 2H, CH_2), 2.00 (2 s, 3H, CH_3CO-), 1.92 (m, 2H, CH_2), 1.08 (s, 9H, tert-butyl).

Cytosine, 5-fluorocytosine, and the other 5-substituted cytosin derivatives w re c upl d with the acetate 57 by the methodology of Vorbruggen and Bennua (J. Org. Chem., 39, 3654, 1974) with modifications. A mixtur of cytosine (0.42 g, 3.80 mmol), hexamet[illegible]silazane (HMDS, 0.54mL, 2.52 mmol),

chlorotrimethylsilane (TMSCl 1.48 mL, 11.6 mmol), potassium nonafluor butanesulfonate (3.08 g, 8.9 mmol), and the acetate 57 (1.04 g, 2.52 mmol) in dry acetonitrile was stirr d at room temperature overnight to afford 0.65g (55%) of 1-[5-O-(tert-butyldiphenylsiyl)-2,3-dideoxy-4-thio-alpha,beta-L-ribofuranosyl]cytosine (58 X=H) as a 4:3 alpha/beta- mixture. The alpha and beta anomers were separated by silica gel column chromatography. Deprotection of 58 (beta anomer) afforded 1-(2,3-dideoxy-4-thio-beta-L-ribofuranosyl)cytosine (59 X=H) in 60% yield: MS m/e 228 (M^++1); ^{1}HNMR (DMSO-d_6) delta 8.05 (d, 1H, H-6), 7.08 (br d, 2H, NH_2, D_2O exchangeable), 6.10 (m, 1H, 1'-H), 5.70 (d, 1H, H-5), 5.20 (br d, 1H, 5'-OH, D_2O exchangeable), 3.58 (m, 1H, 5'-H), 3.52 (m, 2H, 4'-H and 5'-H), 2.20 (m, 1H, 2'-H), 2.04 (m 2H, 2'-H and 3'-H), 1.88 (m, 1H, 3'-H).

EXAMPLE 7

1-(2,3-Dideoxy-4-thio-beta-L-ribofuranosyl)-5-methyl-, -5-ethyl-, -5-vinyl-, -5-bromovinyl-, -5-ethynyl-, -5-fluoro-, -5-chloro-, -5-bromo-, -5-iodouracil, and 1-(2,3-Dideoxy-4-thio-beta-L-ribofuranosyl)uracil

Thymine, uracil, -5-ethyl-, -5-vinyl-, -5-bromovinyl-, -5-ethynyl-, -5-fluoro-, -5-chloro-, -5-bromo-, -5-iodouracil, and other 5-substituted uracil derivatives were coupled with 1-O-acetyl-5-O-(tert-butyldiphenylsilyl)-2,3-dideoxy-4-thio-L-ribofuranose (57) using the same procedure as described in Example 6 to give the respective 5-subsituted pyrimidine nucleosides.

A mixture of the acetate 57 (1.40 g, 3.32 mmol), thymine (0.52 g, 4.20 mmol), HMDS (0.70 mL, 3.32 mmol), TMSCl (1.60 mL, 12.8 mmol) and potassium nonafluorobutanesulfonate (3.50 g, 10.16 mmol) in dry acetonitrile was stirred at 25°C overnight under nitrogen to give 1-[5-O(tert-butyldiphenylsilyl)-2,3-dideoxy-4-thio-alpha,beta-L-ribofuranosyl]thymine (60, X= CH_3) 1.18 g (74%) as a 4:3 alpha/beta anomeric mixture. The alpha/beta anomers were separated by silica gel column chromatography. Deprotection of beta-anomer 60 afforded 1-(2,3)-dideoxy-4-thio-beta-L-ribofuranosyl)thymine (61, X=CH3) in 55% yield: Ms m/e 243 (m^+ +1); ^{1}HMR (DMSO-d_6) delta 11.5 (br s, 1H, NH), 7.74 (s, 1H, 6-H), 6.11 (m, 1H, 1'-H), 5.00 (t, 1-H, 5'-OH, D_2O exchangeable), 3.70 (m, 1-H, 4'-H), 3.65 (m, 2H, 5'-CH_2) 2.20-1.80 (m, 4H, 2'-CH_2 and 3'-CH_2), 1.79 (s, 3H, 5-CH_3).

EXAMPLE 8

2',3'-Dideoxy-4'-thio-beta-L-adenosine, 2',3'-Dideoxy-4'-thio-N-Methyl-beta-L-, -N,N-dimethyl-beta-L-adenosine, 2',3'-Dideoxy-4'-thio-beta-L-inosine, and 2',3'-Dideoxy-4'-thio-beta-L-guanosine

2',3'-Dideoxy-4'-thio-beta-L-adenosin , 2'3'-Dideoxy-4'thio-N-methyl-beta-L-aden sine, 2'3'-Did oxy-4'thi -N,N-dimethyl-beta-L-adenosine, 2',3'-Dideoxy-4'-thio-beta-L-in sine, and 2',3'-Dideoxy-4'-thio-beta-L-guanosine were synthesized by the similar methodology of Secrist et al. (J. Med. Chem., 35, 533, 1992) for the syntheses of 2',3'-dideoxy-4'-thio-D-nucleosides.

Sugar 57 (4.3 g, 10.4 mmol) was coupled with 6-chloropurine (2.4 g, 15.6 mmol) in the presence of diethylaluminum chloride (5.9 mL, 10.6 mmol) in acetonitrile (150 mL) at 0-5°C for 2h, by the procedure of Niedballa and Vobruggen (J. Org. Chem., 39, 3654 1974), to give 2.81 g (53%) of 9-[5-O-(tert-butyldiphenlsilyl)-2,3-dideoxy-4-thio-alpha,beta-L-ribofuranosyl]-6-chloropurine as a 1:1 alpha/beta anomeric mixture. The alpha and beta anomers were separated by silica gel column chromatography. The beta-anomer 62 was treated with saturated ammonia/methanol and then deprotected with 1 M tetrabutylammonium fluoride and THF to afford 2',3'-dideoxy-4'-thio-beta-L-adenosine (63, R'=R"=H): ^{1}HNMR (DMSO-d_6) delta 8.30 (s, 1H, 2-H), 8.10 (s, 1 H, 8-H), 7.30 (s, 2H, NH_2, D_2O exchang - able), 6.12 (m, 1H, 1'-H), 5.11 (br s, 1H, 5'-OH, D_2O exchange-able), 3.70 (m, 3H, 5'-CH_2, 4'-H), 2.42 (m, 2H, 2'-CH_2), 2.13 (m, 1H, 3'-H), 2.00 (m, 1H, 3'-H).

Compound 62 was deprotected with 1 M tetrabutylammonium fluoride and THF to yield 9-(2,3-dideoxy-4'-thio-beta-L-ribofuranosyl)-6-chloropurine (64). Alkaline hydrolysis (Fujimori, et al., Nucleosides & Nucleosides, 11, 341, 1992) of the 6-chloro moiety in compound 64 afforded 2',3'-dideoxy-4'-thio-beta-L-inosine (65) in 45% yield: MS m/e 253 (m^++1); ^{1}HNMR (D_2O) delta 8.52 (s, 1H, 2-H), 8.19 (s, 1H, 8-H), 6.10 (m, 1H, 1'-H), 3.94 (m, 1H, 5'-H), 3.75 (m, 2H, 5'-H, 4'-H), 2.52 (m, 2H, 2'-CH_2), 2.30 (m, 1H, 3'-H) 1.92 (m, 1H, 3'-H).

2',3'-Dideoxy-4'-thio-beta-L-guanosine (68) was synthesized from acetate (57) by the similar methodology as described for the synthesis of compound 65: MS m/e 268 (m^++1): ^{1}HNMR (DMSO-d_6) delta 10.7 (br s, 1H, NH, D_2O exchangeable), 8.01 (s, 1H, 8-H), 6.55 (s, 2H, NH_2, D_2O exchangeabl), 5.90 (m, 1H, 1'-H), 5.09 (br s, 1 H, 5'-OH, D_2O xchangeable), 3.70 (m, 1H, 4'-H), 3.50 (m, 2H, 5'-H), 2.36 (m, 2H, 2'-H), 2.17 (m, 1H, 3'-H), 1.93 (m, 1H, 3'-H).

EXAMPLE 9

2',3'-Dideoxy-4'-thio-2-chloro-beta-L-adenosine, -2-amino-beta-L-adenosine, -2-fluoro-beta-L-adenosin , -2-chloro-N-methyl-beta-L-adenosine, -2-chloro-N,N-dimethyl-beta-L-adenosine, -2-bromo-beta-L-adenosine, -2-bromo-N-methyl-beta-L-adenosine and -2-bromo-N,N-dimethyl-beta -L-adenosine

2',3'-Dideoxy-4'-thio-2-chloro-beta-L-adenosine, 2-amino-beta-L-adenosine, -2-fluoro-beta-L-adenosine, -2-chloro-N-methyl-beta-L-adenosine, -2-chloro-N,N-dimethyl-beta-L-adenosine, -2-bromo-beta-L-adenosine, -2-bromo-N-methyl-beta-L-adenosine and -2-bromo-N,N-dimethyl-beta-L-adenosine and other beta-L-adenosine derivatives were synthesized as set forth in Scheme 11.

9-[5-O-(tert-Butyldiphenylsilyl)-2,3-dideoxy-4-thio-beta-L-ribofuranosyl]-2,6-dichloropurine (69) was synthesized from the acetate 57 and 2,6-dichloropurine by the similar methodology as described for the synthesis of compound 62 in an approximate 2:3 alpha/beta anomer ratio in 60% yield. The alpha and beta anomers were separated by silica gel column chromatography. Compound 69 was treated with saturated ammonia/methanol and then deprotect d with 1 M tetrabutylammonium fluoride in THF to provide 2',3'-dideoxy-4'-thio-2-chloro-beta-L-adenosine (70 R'=R"=H) in 52% yield: MS m/e 286 (m^++1); ^{1}HNMR (DMSO-d_6) delta 8.46 (s, 1H, 2-H), 7.82 (br s, 2H, NH_2, D_2O exchangeable), 6.10 (m, 1H, 1'-H), 5.10 (m, 1H, 5'-OH, D_2O exchangeable), 3.74 (m, 1H, 4'-H), 3.60 (m, 2H, 5'-H), 2.42 (m, 2H, 2'-H), 2.13 (m, 1H, 3'-H), 2.02 (m, 1H, 3'-H).

2',3'-Dideoxy-4'thio-2-bromo-alpha,beta-L-adenosine (72, R'=R" =H) was synthesized by coupling the acetate 57 and 2,6-dibromopurine, followed by treatment of the respective amine by the same methodology as described for the synthesis of compound 70.

Compound 69 was treated with lithium azide to give the diazido nucleoside 73, which was then reduced with lithium aluminium hydride (LAH) to produce 9-[5-O-(tert-butydiphenylsilyl)-2,3-dideoxy-4-thio-alpha,beta-L-ribofuranosyl]-2,6-diaminopurine (74). Compound 74 was deprotected with tetrabutylammonium fluoride in THF to yield 2',3'- dideoxy-4'-thio-2-amino-alpha,beta-L-adenosine (75), which was then converted to 2',3'-dideoxy-4'-thio-2-fluoro-alpha,beta-L-adenosine (76) by r action with sodium nitrit and HBF_4.

II. Biological Activity

A. Anti-HBV Eff cts

The biological activity of the present compounds was assessed as described by Doong, S-L, et al., Proc. Natl. Acad. Sci. U.S.A 88, 8495-8499 (1991). The human hepatoma cell line carrying the HBV (designated 2.2.15) kindly provided by Dr. G. Acs was used in the study. Price, et al., Proc. Natl. Acad. Sci. U.S.A. 86, 8541 (1989). Briefly, six day-old cultures were treated with varying concentrations of the drug in the culture medium (Minimum essential medium with Earl's salts and 10% fetal bovine serum). The drug was left in the culture medium for a period of 3 days after which period the medium was aspirated and fresh medium containing the same concentration(s) of the drug was added. At the end of the subsequent 3 day period the culture medium was harvested. The culture medium was processed for obtaining the virions by the polyethylene glycol precipitation method (Doong, et al., supra). Viral DNA thus recovered from the secreted particles was subjected to Southern analysis. Inhibition of the viral replication was determined by the comparison of the viral DNA from drug-treated versus control cultures not treated with the drug.

To determine the cellular toxicity of the present compounds, the T-lymphoblastoic cell line (CEM) was used. Cells were subjected to varying concentrations of the drug(s) and cell numbers were determined 3 days post treatment by the method described by Chen, C-H and Cheng, Y-C J. Biol. Chem., 264, 11934 (1989). Concentrations of the drug which would result in 50% killing of the cell populations were determined from the plot generated by representing cell numbers corresponding to the individual drug concentrations.

The effects of the various drug concentrations on mitochondrial DNA (mt DNA) was evaluated by the method described by Chen and Cheng, supra. CEM cells treated with varying concentrations of the drug were collected by centrifugation. After washing the cells with phosphate buffered saline, cells were lysed by suspending the cells in 10 mM Tris-HCl (pH 7.0) and repeating fr eze thaw cycles. Th resulting cells were then subj cted to RNase A treatment at a final enzyme concentration of 10 ug/ml, followed by proteinase K treatment (100 ug/ml) for 1 hour. The DNA thus obtained by this procedure was then immobilized on nylon membrane aft r the addition of 0.8 vol . . T and boiling

for 10 minut s. Hybridization of the resulting DNA to a mt DNA specific probe was perform d by f ll wing the method of Doong, S-L, supra and aut radi graphy was also perform d. Quantitative estimates w r obtain d by scanning densitom ter. Th blots were stripped of the mtDNA probe and rehybridized to human Alu sequence probe to determine the amounts f DNA f r normalization and estimation of absolute amounts of the mt DNA.

B. Anti-HIV Effects

Drug susceptibility assay for determining the effectiveness of the compounds of the present invention against HIV in MT-2 cells is a modification of the assay described in Mellors, et al., Molecular Pharmacology, 41, 446 (1992). Drug-mediated inhibition of virus-induced cell toxicity was measured by the A_{595} of MTT ([3-I 4,5-dimethyl thiazol-2-yl]-2,3-diphenyltetrazolium bromide) (Sigma M-2128). Triplicate wells of a 96 well plate which contains 1 X 10^4 MT2 cells (AIDS-repository) were infected with HIV-1 (HTLV-IIIB Strain-R.C. Gallo) at a multiplicity of 0.01 $TCID_{50}$/cell. MT-2 cells in RPMI 1640 media supplemented with 10% dialysized fetal bovine and 100 ug/ml Kanamycin were infected with virus and immediately added to serial dilution of the drug. After 5 days, 20 ul of MTT dye (2.5 mg/ml in PBS) was added per well. At the end of a four hour incubation period 150 ul of acidified 2-propanol with NP-40 non-ionic detergent was added. After the crystals of dye dissolve (usually 1-2 days), the plates are read on a micro-plate reader. Using this MTT-dye reduction method (as set forth by Larder, et al., Antimicrobial Agents and Chemotherapy, 34, 436 (1990), th percentage of protection can be calculated using the formula [(a-b/c-b) X 100] in which a=A_{595} of drug treated cells, b is the number of non-drug infected cells and c is the A_{595} of the non-drug infected cells.

The ID_{50} values for anti-HIV activity of the compound ß-L-FddC and other compounds are presented in Table 1, below.

C. Results of Biological Testing

Analysis of the viral replication of HBV from the secreted particles reveal d that the DNA replication was ffi-ciently inhibited by both ß-L-ddC and ß-L-FddC. Th ID_{50} con-centration r quir d to inhibit the viral r plication by thess compounds was 0.01 uM. Th c llular cytotoxicity of thes com-

pounds as compared to ddC was also considerably less as evidenced by the Table 1 set forth below. It is interesting to not that these compounds have several fold higher activity against HBV with minimal cellular effects, an unexpected result. ddC on the other hand, was much more cytotoxic than either ß-L-ddC or ß-L-FddC. In addition, ddC also was shown to exhibit significant effects on host mitochonrial DNA. It is expected that ß-L-ddC and ß-L-FddC would have significantly lower adverse effects on the mitochondrial DNA than ddC as concentrations as high as 100 uM of ß-L-ddC or ß-L-FddC were not inhibitory in the assay. This result is particularly significant inasmuch as ddC exhibits dose limiting toxicity in causing severe neuropathy, a condition which is believed to be at least in part caused by inhibition of host mitochondrial DNA. Based upon these results, ß-L-ddC and ß-L-FddC are extremely interesting compounds with significant anti-HBV activity, and a clear advance in the art. The data on the anti-HBV effects of ß-LddC and ß-L-FddC are summarised in Tabl 1, below.

Separately, utilizing the above-described procedure, ß-L-FddC was screened for anti-HIV activity. ß-L-FddC was tested and compared to other compounds, and in particular, DDC, ß-L-ddC, alpha-L-FddC, ß-L-ddSC and alpha-L-ddSC. The results are presented in Table 1, below.

Based upon the results set forth in Table 1, ß-L-FddC exhibited anti-HIV activity which was significantly more effective than ddC, a known anti-HIV agent. The ID_{50} concentration f ß-L-FddC required to inhibit viral replication in this assay was 0.007 micromolar. For ddC, the ID_{50} concentration was determined to be 0.028 micromolar, a 4-fold difference. The cellular cytotoxicity of ß-L-FddC as compared to ddC was also considerably less as evidenced by the Table 1 data set forth below. It is interesting to note that this compound has several fold higher activity against HIV with significantly less cellular toxicity, an unexpected result. ddC, on the other hand, was more cytotoxic than ß-L-FddC and yet, less active against HIV. In addition, ddC was shown to exhibit dramatic effects on host mitochondrial DNA, whereas ß-L-FddC had relatively little effect. It is expected that ß-L-FddC would have significantly lower adverse effects on the host mitochondrial DNA than ddC as concentrations as high as 100 uM of ß-L-FddC w r not inhibitory in the assay. The data on the effects of ß-L-FddC are summarised in Table 1, below and compared with ddC, ß-L-ddC, alpha-L-FddC, ß-ddSC and alpha-ddSC. The implications for ß-L-FddC as an anti-HIV agent are clear as

the results presented herein evidence ß-L-FddC to be an agent which xhibits exceptional anti-HIV activity and virtually no toxicity associated with dose limiting neuropathy. This stands in contrast to the presently available ddC.

Table 1
Anti-HBV and Anti-HIV Activities of L-2',3'-Dideoxy Nucleoside Analogs

Compound	Cytotoxicity CEM Cells	ID_{50}(uM) Anti-Mitochondrial DNA	Anti-HBV	Anti-HIV
ddC	28	0.022	2.8	0.028
ß-L-ddC	70	>100	0.01	0.35
ß-L-FddC	67	>100	0.01	0.007
alpha-L-FddC	>100	ND	0.5	0.3
ß-L-ddSC	>100	ND	>0.5	70
alpha-L-ddSC	>100	ND	>0.5	>>100

ND- not determined

ddC- 1-(2,3-dideoxy-beta-D-ribofuranosyl)cytosine

ß-L-ddC- 1-(2,3-dideoxy-beta-L-ribofuranosyl)cytosine

ß-L-FddC- 1-(2,3-dideoxy-beta-L-ribofuranosyl)-5-fluorocytosine

alpha-L-FddC- 1-(2,3-dideoxy-alpha-L-ribofuranosyl)-5-fluorocytosine

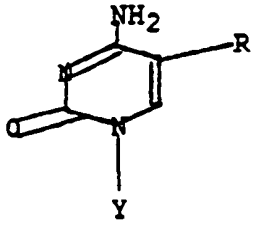
ß-L-ddSC- 1-(2,3-dideoxy-4-thio-beta-L-ribofuranosyl)cytosine

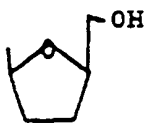
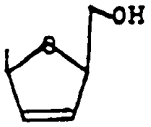
alpha-L-ddSC- 1-(2,3-dideoxy-4-thio-alpha-L-ribofuranosyl) cytosine

It is to be understood by those skilled in the art that the foregoing description and examples are illustrative of practicing the present invention, but are in no way limiting. Variations of the detail presented herein may be made without departing from the spirit and scope of the present invention as defined by the following claims.

Claims:

1. A compound according to the structur :

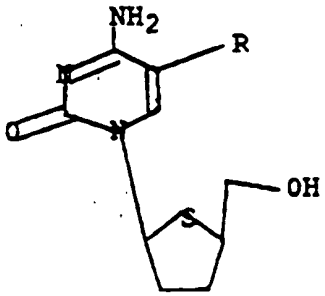


where Y is  or 

and R is F, Cl, Br, I or CH_3.

2. The compound according to claim 1 where R is F.

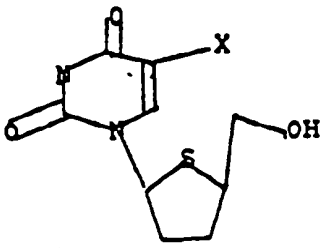
3. A compound according to the structure:

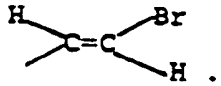


where R is H, F, Cl, Br, I or CH_3.

4. The compound according to claim 3 where R is H.

5. A compound according to the structure:

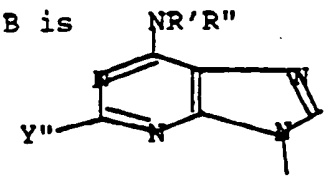
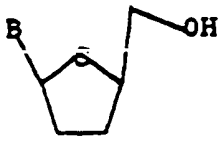
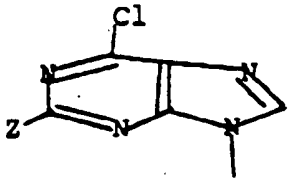
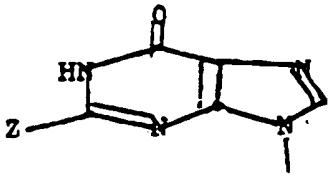


where X is H, F, Cl, Br, I, CH_3, -C≡CH, $-HC=CH_2$ or  .

6. The compound according to claim 5 where X is CH_3 or F.

7. The compound according to claim 6 where X is CH_3.

8. A compound according to the structure:

where B is  ,  ,  or 

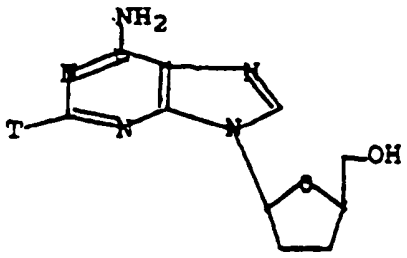
R′ is H or CH_3;
R" is H or CH_3;
Y" is H, F, Br, Cl or NH_2 when R′ and R" are H and
Y" is H when at least one of R′or R" is CH_3;
and Z is H or NH_2.

9. The compound according to claim 8 wherein R′ is H.

10. The compound according to claim 8 wherein R" is H.

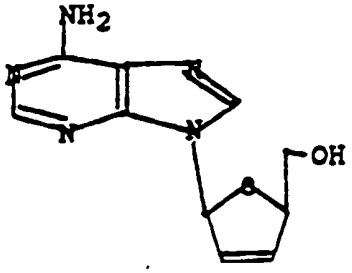
11. The compound according to claim 9 wherein R′ is H, R" is H and Z is H.

12. A compound according to the structure:

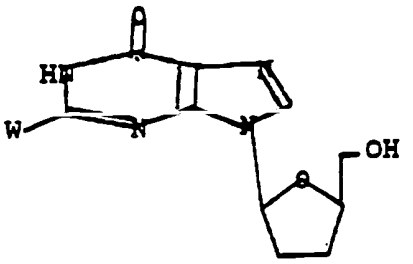


where T is F, Cl, Br or NH_2;

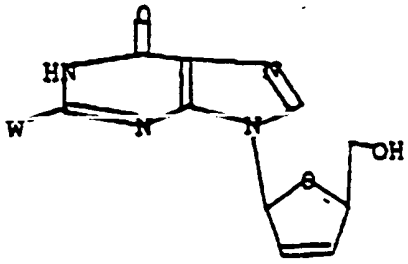
13. A compound according to the structure:



14. A compound according to the structure:

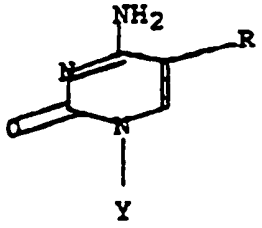


or

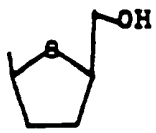


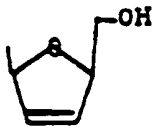
where W is X or NH_2.

15. A method for inhibiting the growth or replication of Hepatitis B virus comprising exposing said virus to an inhibitory effective concentration of a compound according to the structure:

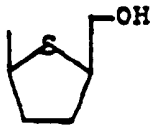


where Y is





or



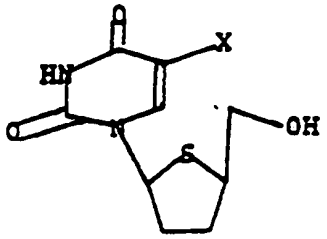
and R is H, F, Cl, Br, I or CH_3.

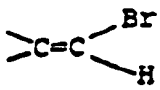
16. The method according to claim 15 where R is H or F.

17. The method according to claim 15 where R is H.

18. A method for inhibiting the growth or replication of Hepatitis B virus comprising exposing said virus to an inhibitory

effectiv c ncentration of a c mpound according to the structure:

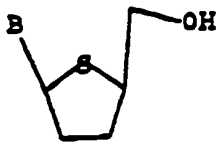


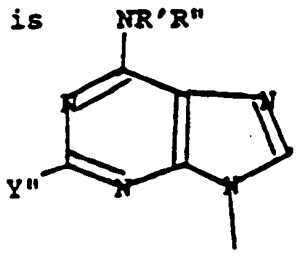
where X is H, F, Cl, Br, I, CH_3, -C≡CH, -HC=CH_2 or  .

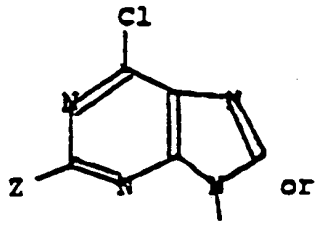
19. The method according to claim 18 where X is CH_3 or F.

20. The method according to claim 18 where X is CH_3.

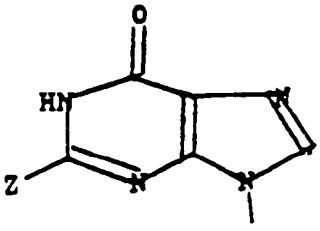
21. A method for inhibiting the growth or replication of Hepatitis B virus comprising exposing said virus to an inhibitory effective concentration of a compound according to the structure:



where B is 



or



R′ is H or CH_3;

R" is H or CH_3;

Y" is H, ., ..., Cl or NH_2 when R′ and R" are H and

Y" is H when at least one of R′or R" is CH_3;

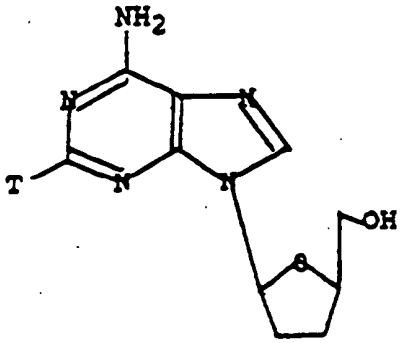
and Z is H or NH_2.

22. The method according to claim 21 wherein R' is H.

23. The method according to claim 21 wherein R" is H.

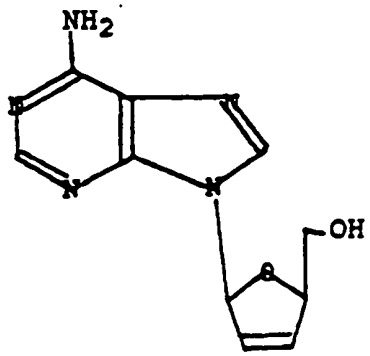
24. The method according to claim 21 wherein R' is H, R" is H and Z is H.

25. A method for inhibiting the growth or replication of Hepatitis B virus comprising exposing said virus to an inhibitory effective concentration of a compound according to the structure:

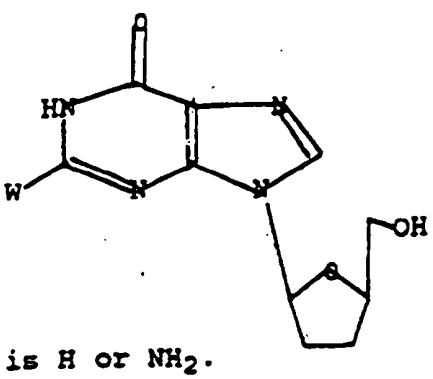


where T is H, F, Cl, Br or NH_2;

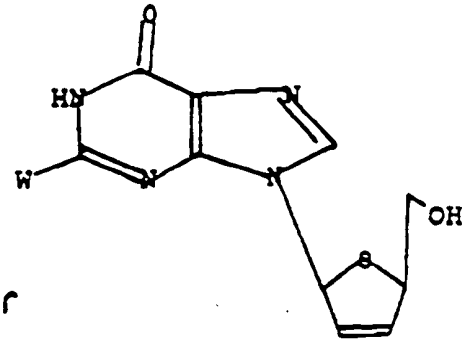
26. A method for inhibiting the growth or replication of Hepatitis B virus comprising exposing said virus to an inhibitory effective concentration of a compound according to the structure:



27. A method for inhibiting the growth or replication of Hepatitis B virus comprising exposing said virus to an inhibitory effective concentration of a compound according to the structure:

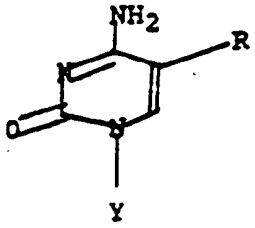


or

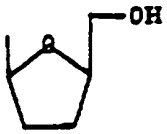


where W is H or NH_2.

28. A method for inhibiting the growth or replication of human immunodeficiency virus comprising exposing said virus to an inhibitory effective concentration of a compound according to the structure:

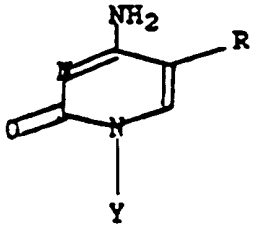


where Y is

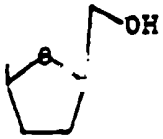


and R is F.

29. A method for treating a patient suffering from an infection caused by the human immunodeficiency virus comprising administering to said patient a therepeutically effective concentration of a compound according to the structure:



where Y is



and R is F.

30. The method according to claim 29 wherein said compound is administered in combination with a pharmaceutically acceptable additive or excipient.

31. The method according to claim 30 wherein said compound is administered in oral dosage form.

32. The method according to claim 29 wherein said compound is administered in parenteral dosage form.

FIGURE 1 - SCHEME 1

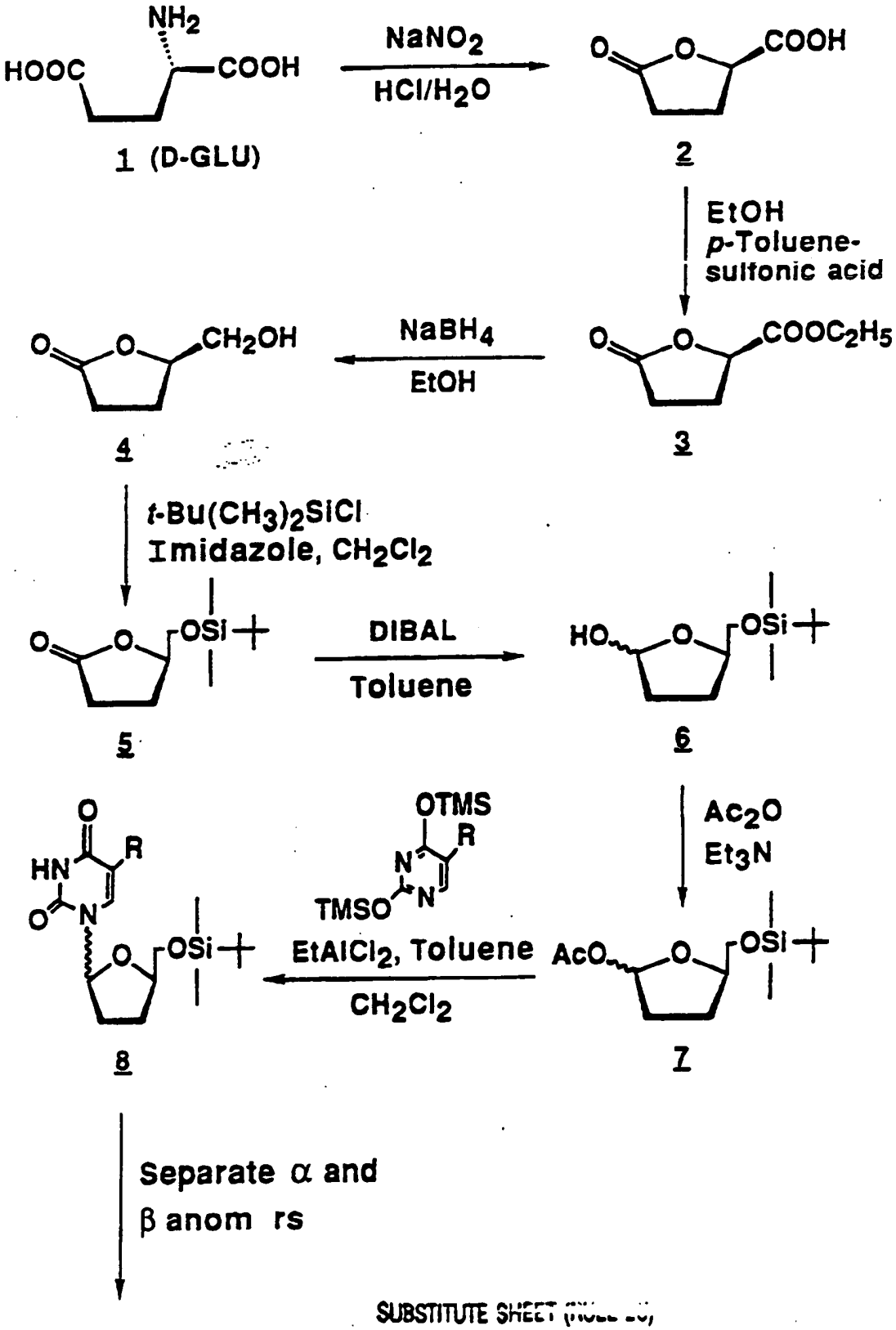


FIGURE 1 - SCHEME 1, CONTD.

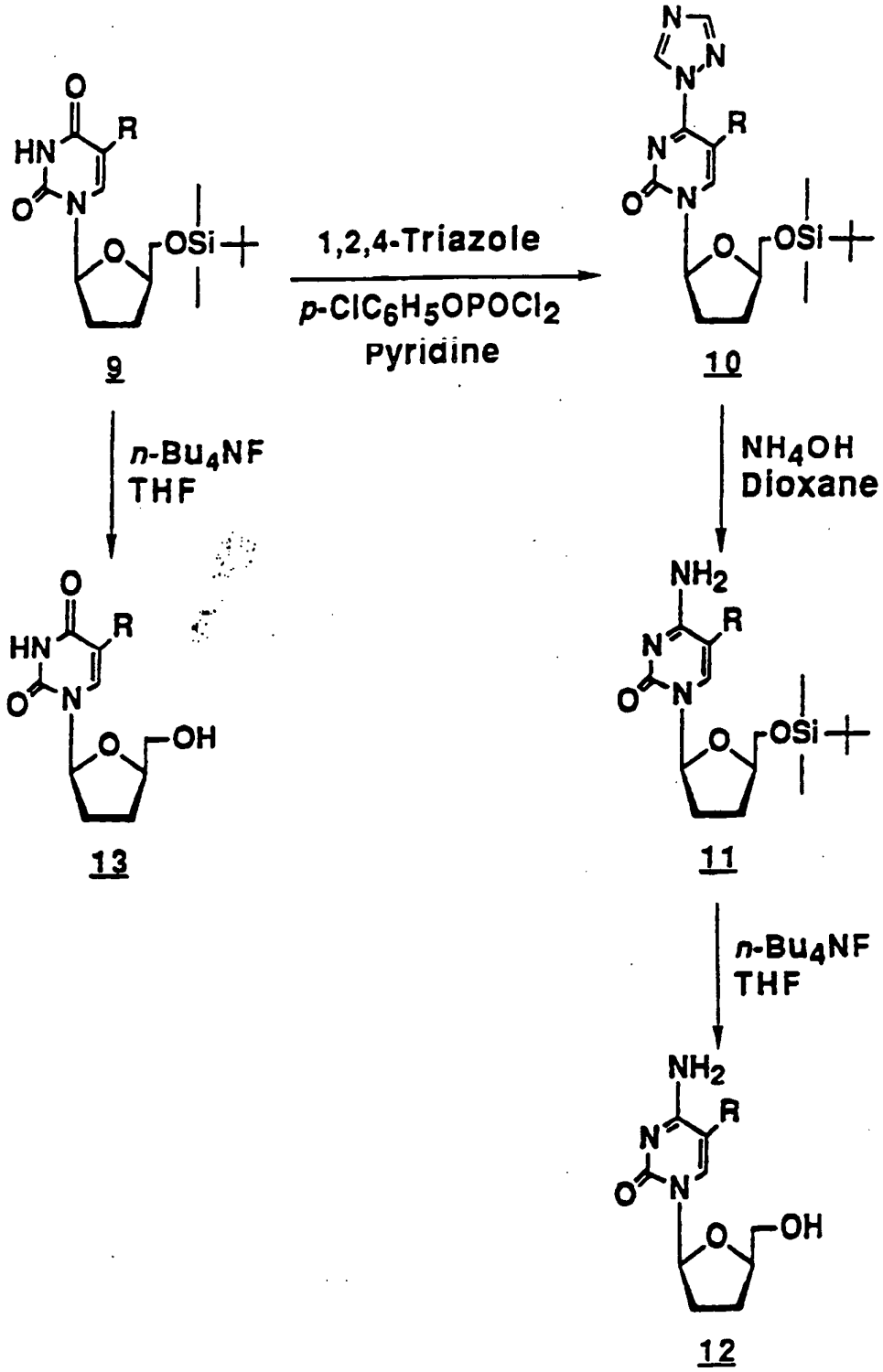
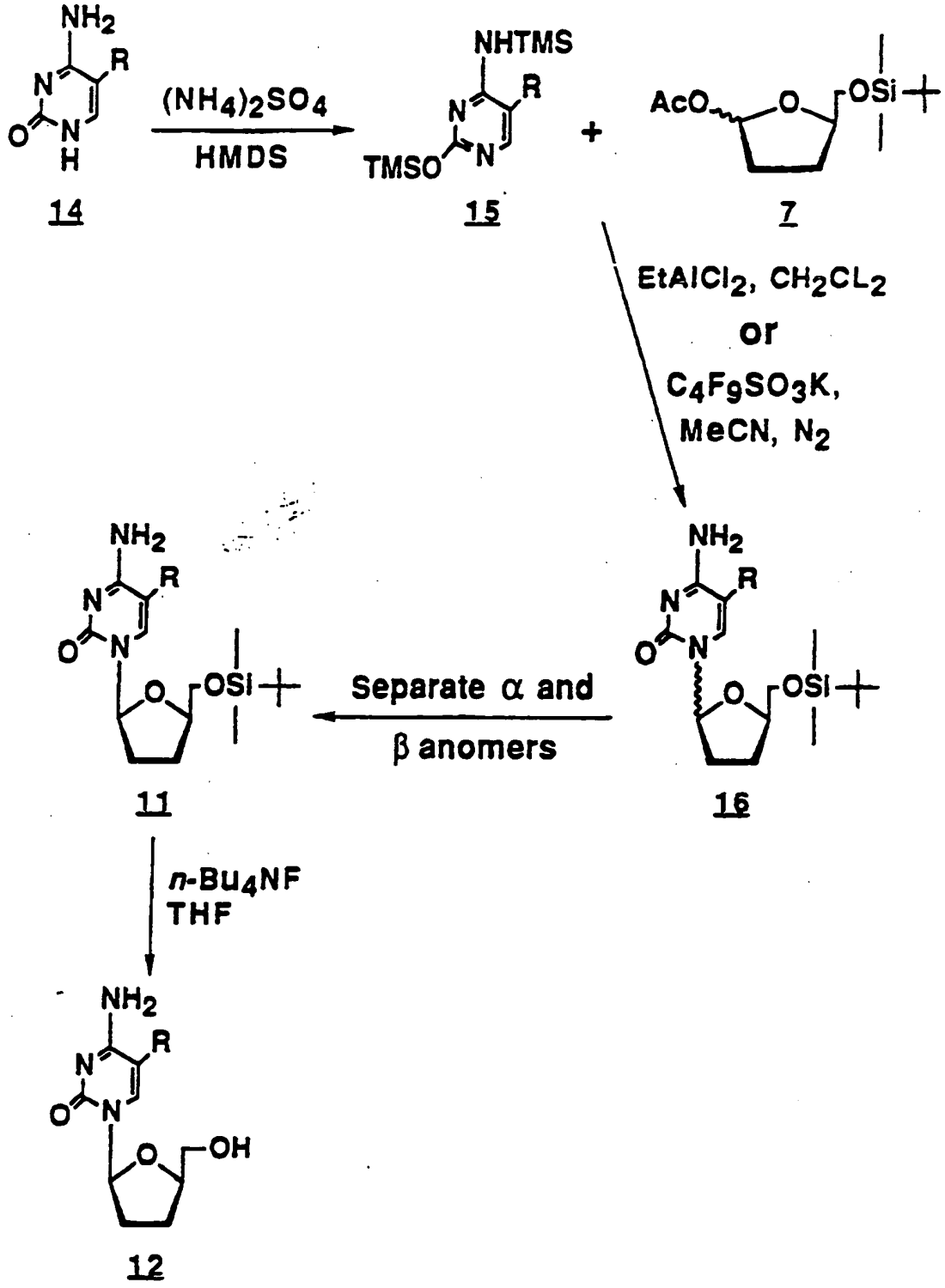


FIGURE 2 - SCHEME 2



R = H, F, Cl, Br, I, CH_3, etc.

FIGURE 3 - SCHEME 3

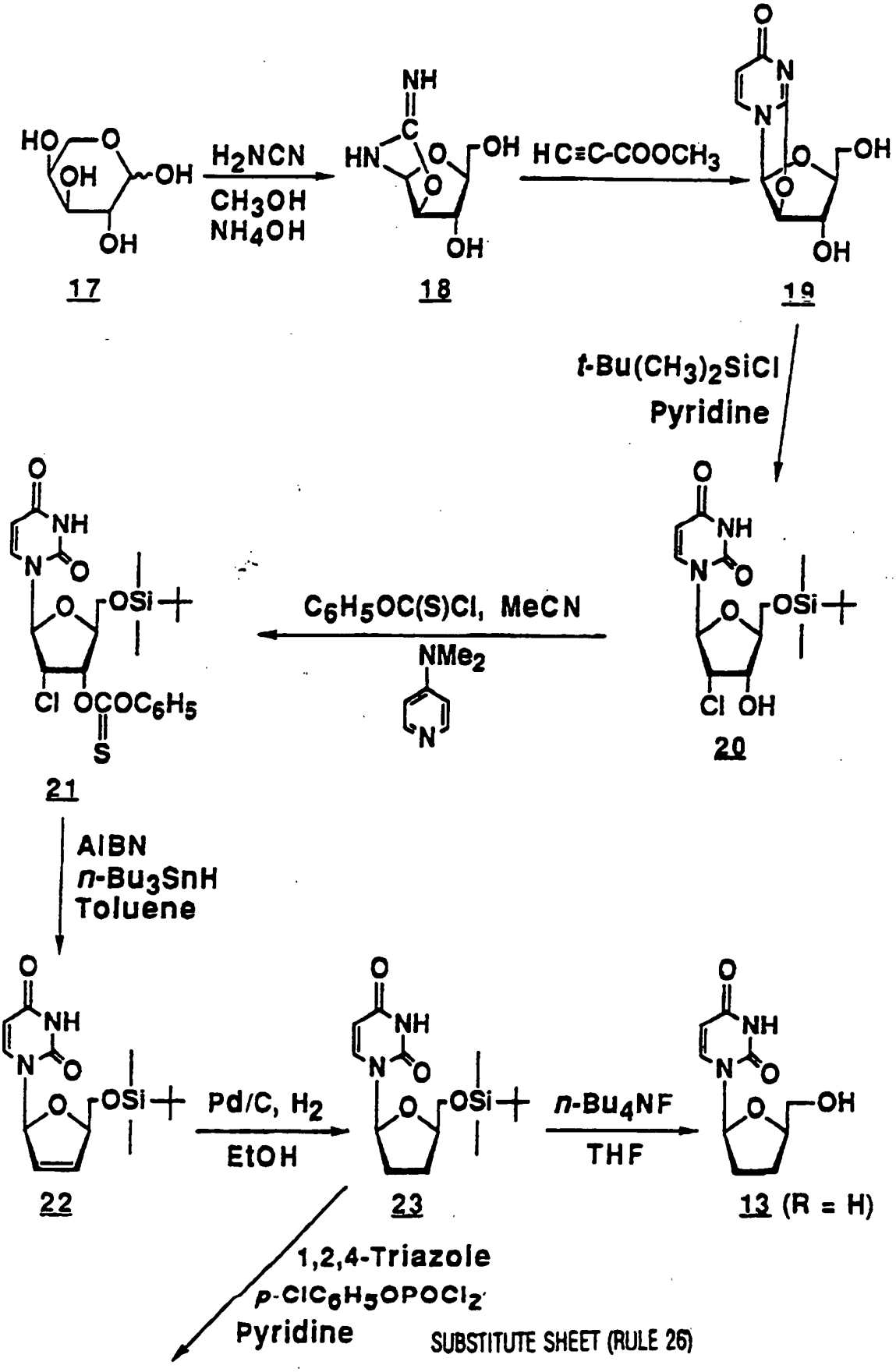


FIGURE 3 - SCHEME 3, CONTD.

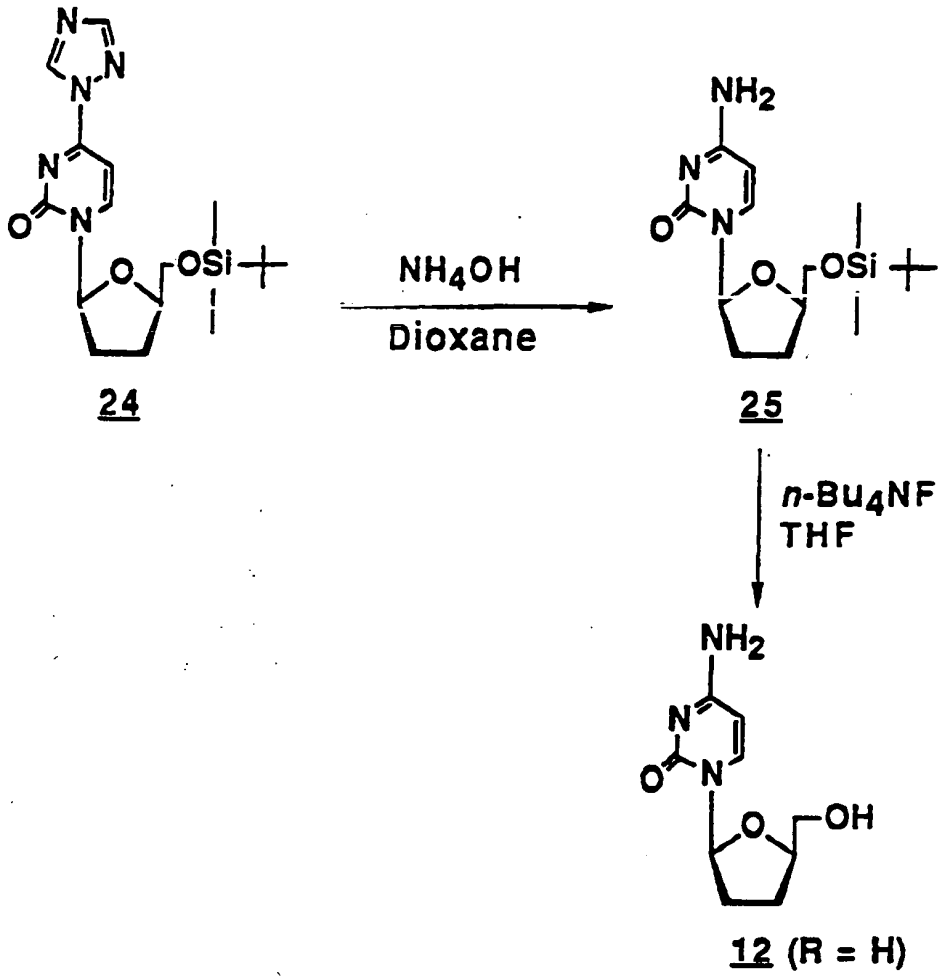


FIGURE 4 - SCHEME 4

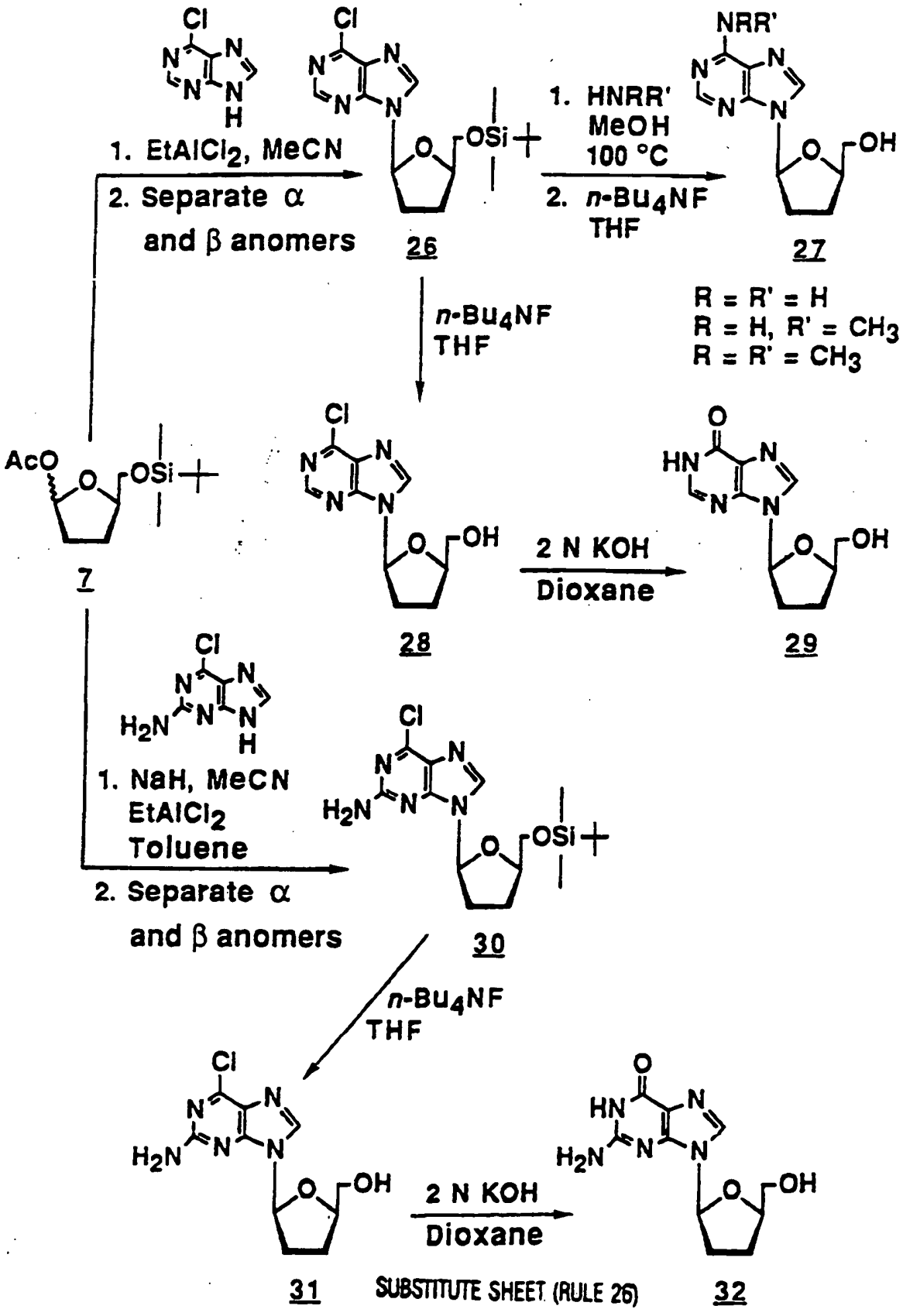


FIGURE 5 - SCHEME 5

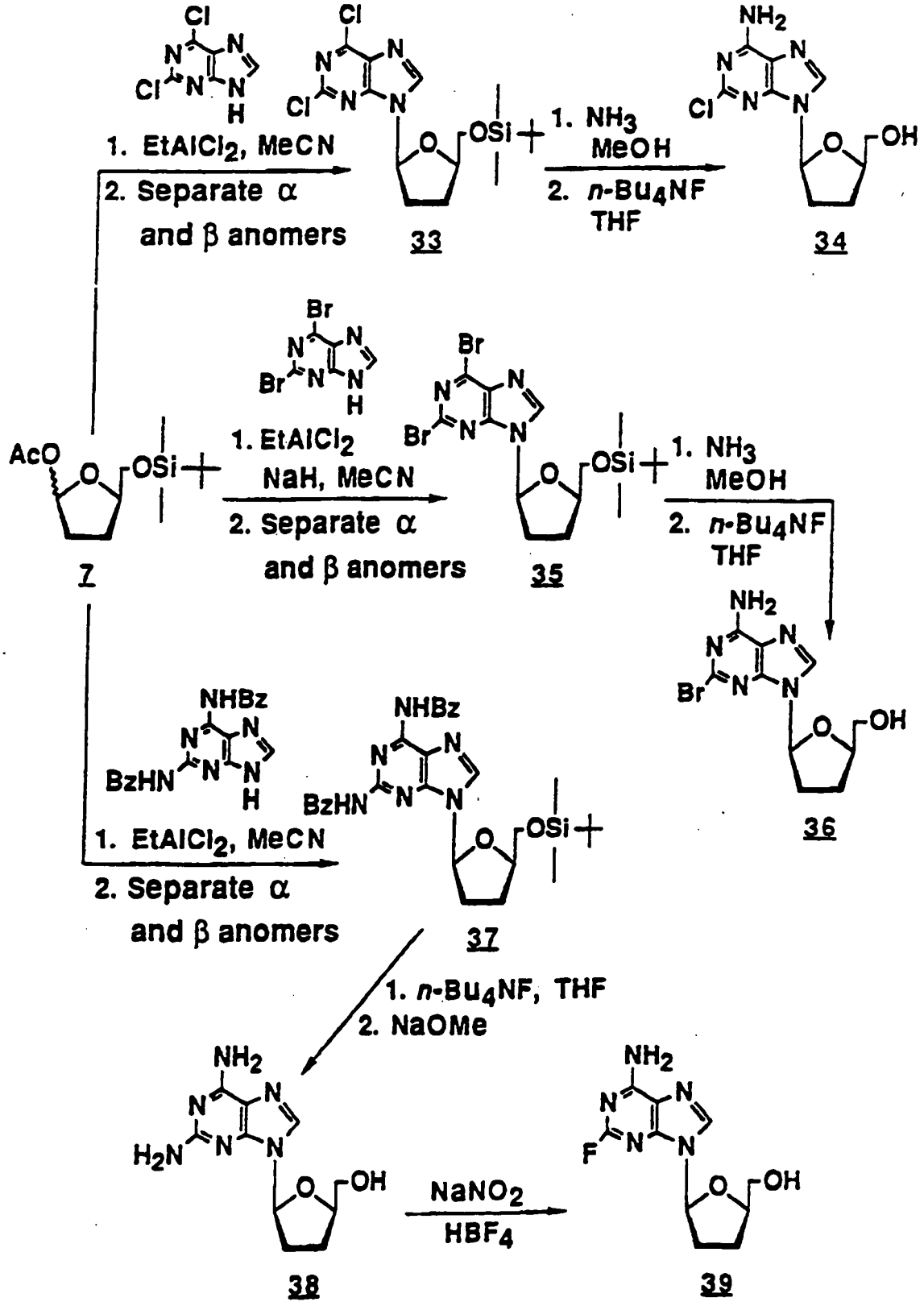
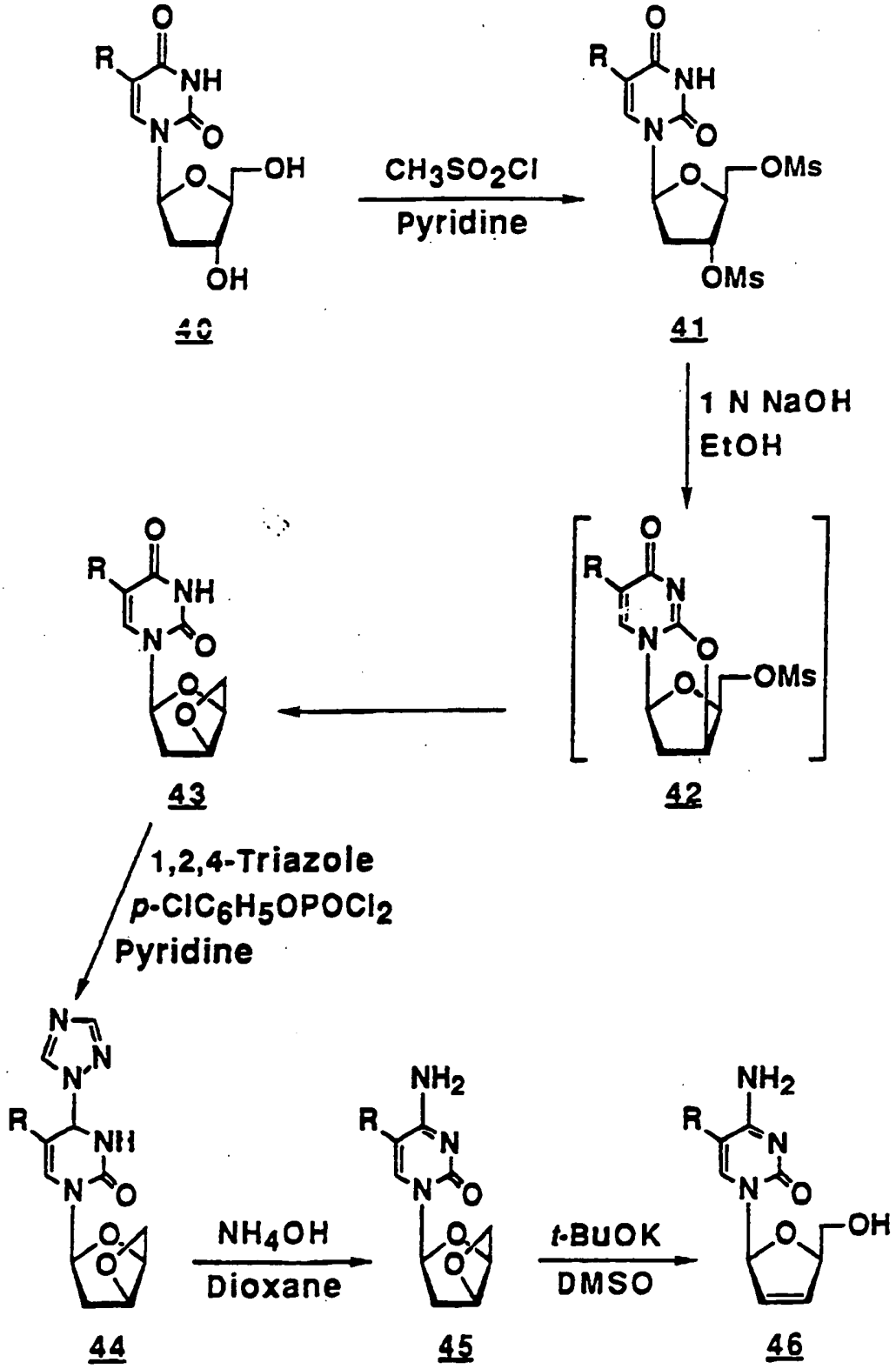


FIGURE 6 - SCHEME 6



R = H, F, Cl, Br, I, CH_3, tc.

FIGURE 7 - SCHEME 7

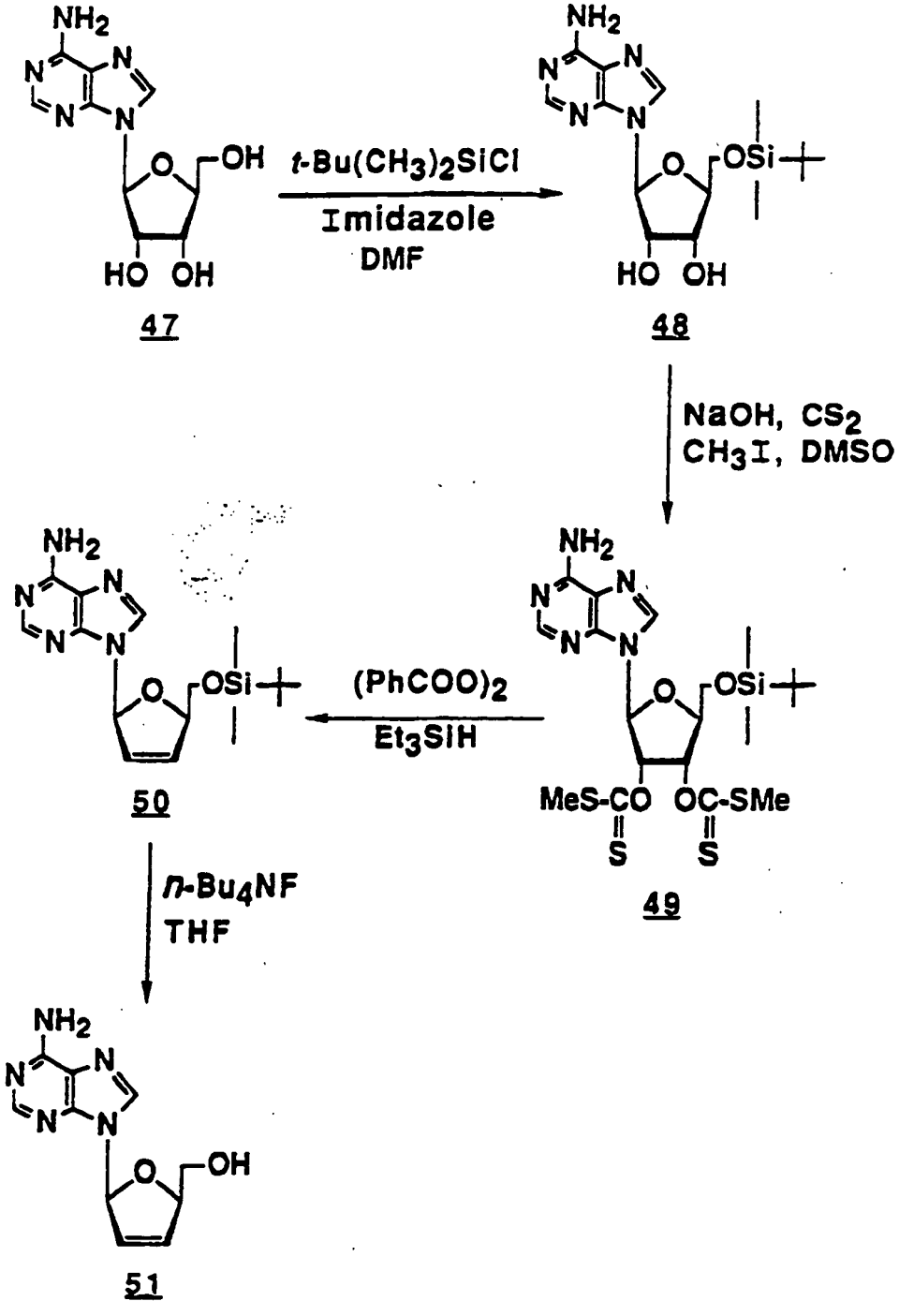
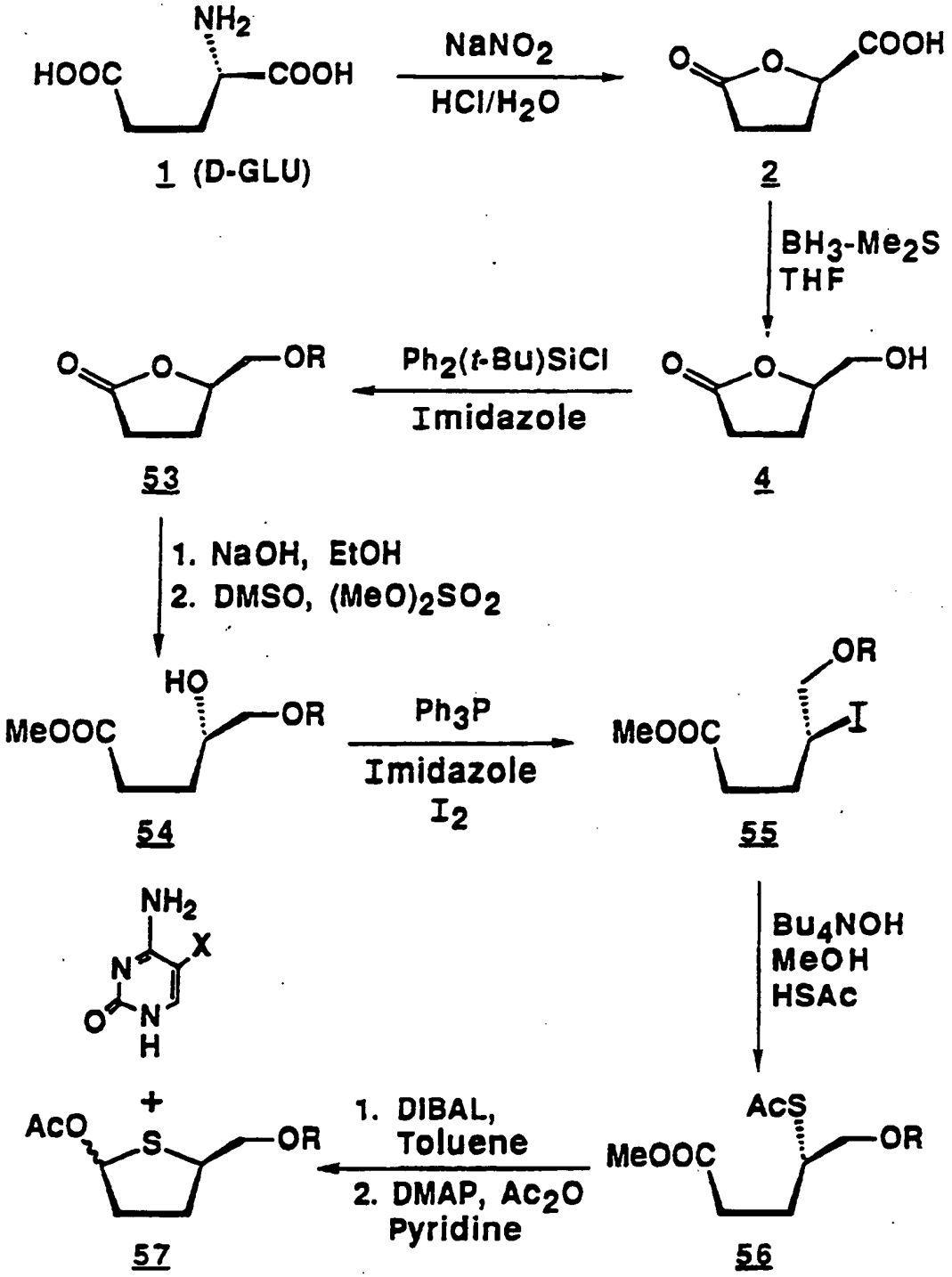


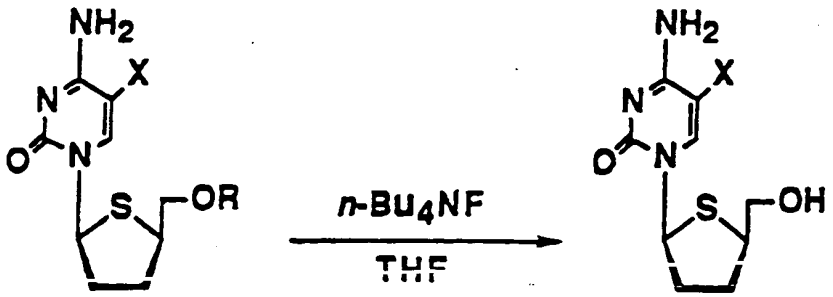
FIGURE 8 - SCHEME 8



R = -Si(*t*-Bu)Ph_2

X = H, F, Cl, Br, I, CH_3, etc.

FIGURE 8 - SCHEME 8, CONTD.

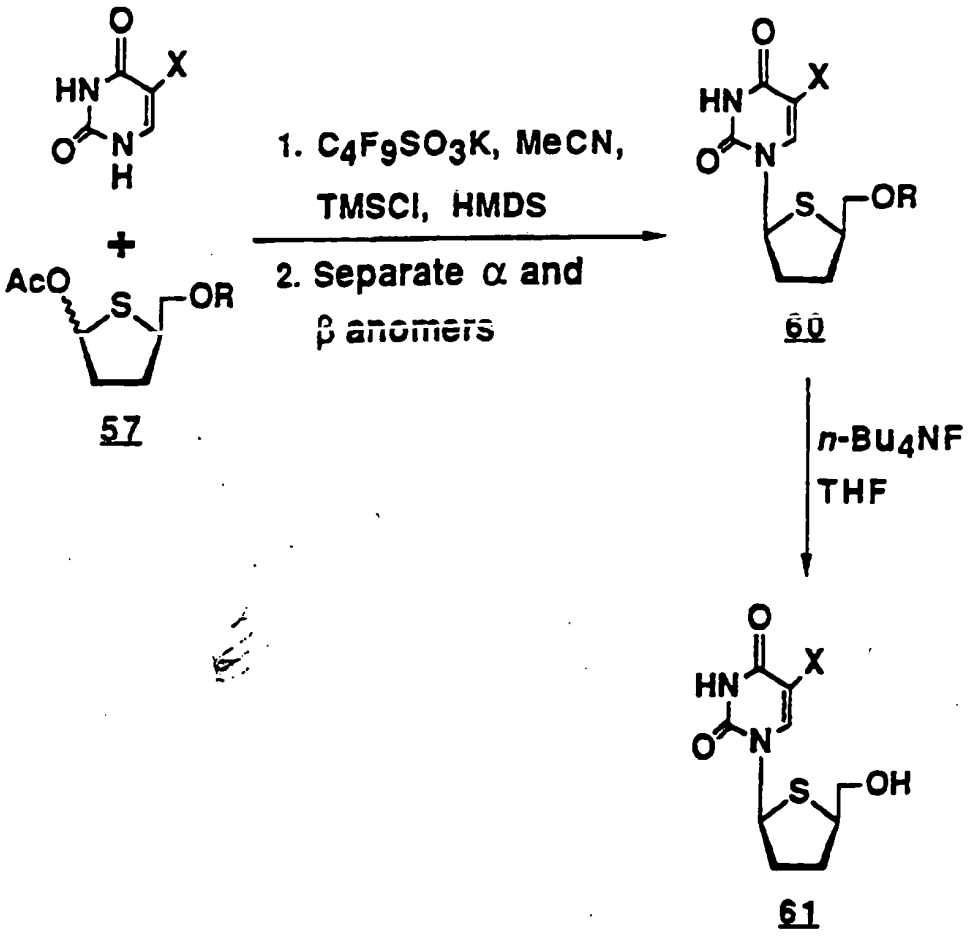


58 59

R = -Si(*t*-Bu)Ph_2

X = H, F, Cl, Br, I, CH_3, etc.

FIGURE 9 - SCHEME 9



R = -Si(*t*-Bu)Ph_2

X = CH_3, Et, F, Cl, Br, I,

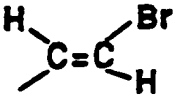
C≡CH, $HC{=}CH_2$, 

FIGURE 10 - SCHEME 10

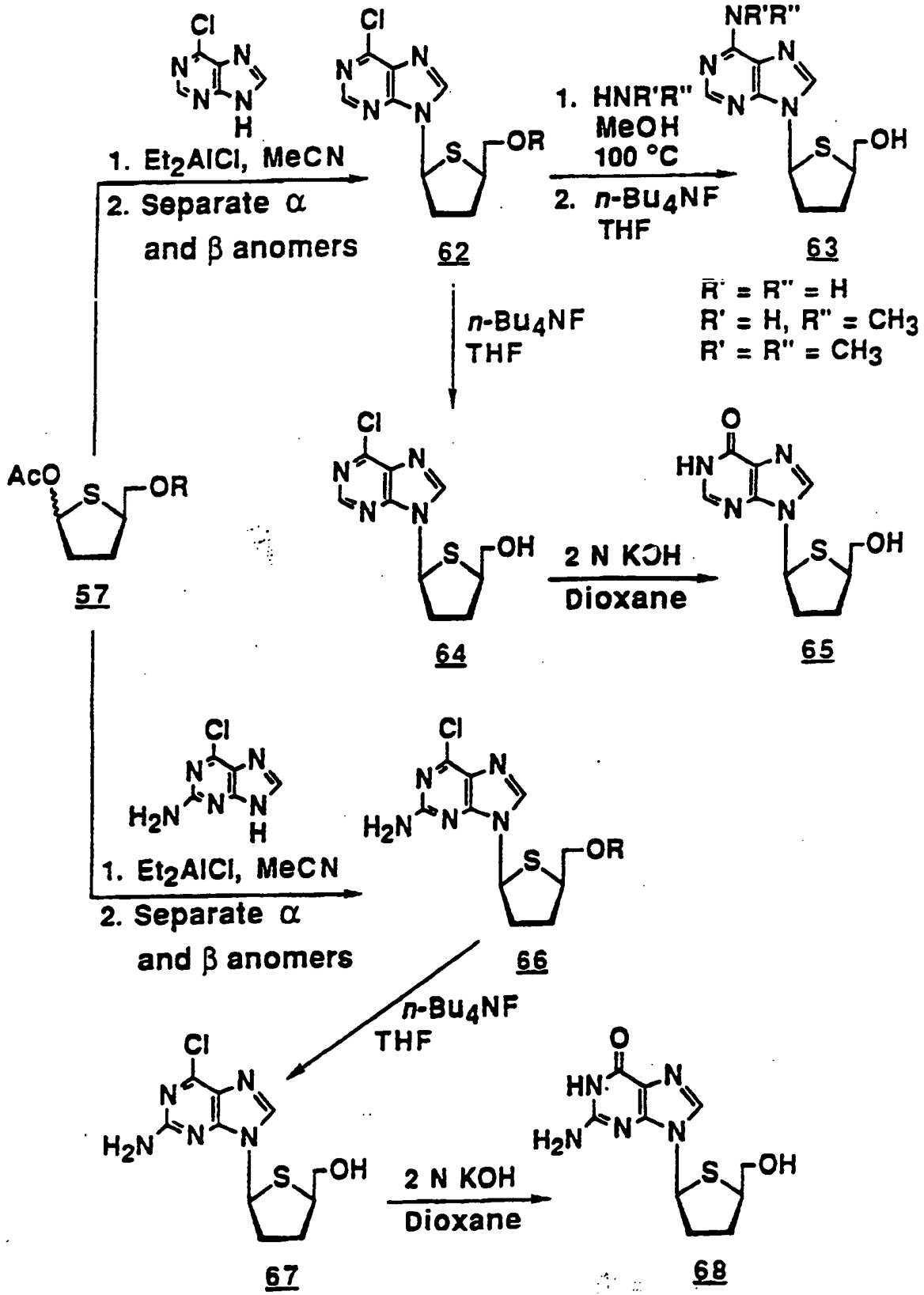
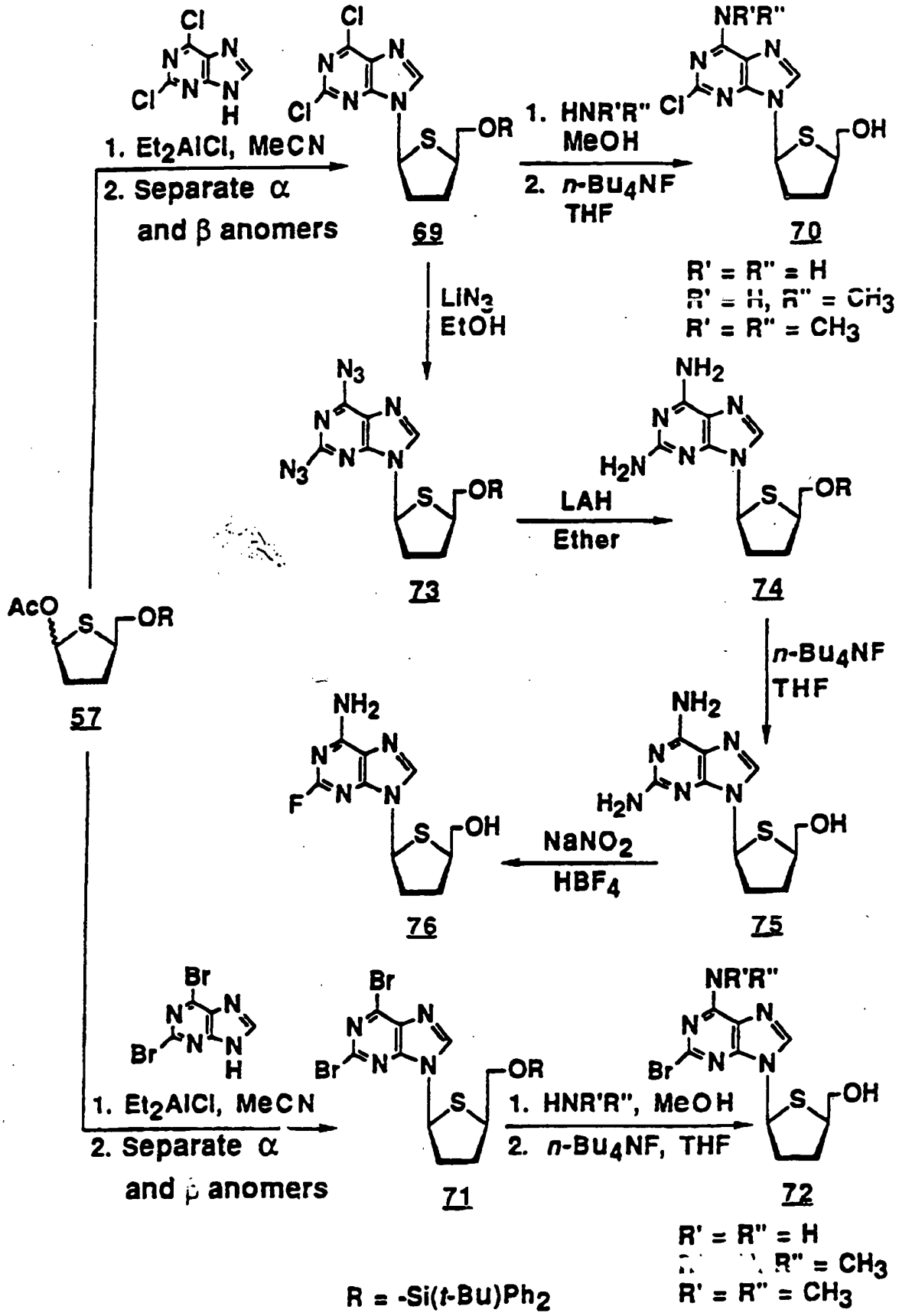


FIGURE 11 - SCHEME 11



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/05790

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61K 31/70; C07H 19/00
US CL :514/46, 47, 49, 50; 536/4.1, 27.14, 28.2; 544/264
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/46, 47, 49, 50; 536/4.1, 27.14, 28.2; 544/264

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS ON LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X/Y	US, A, 4,788,181 (DRISCOLL ET AL.) 29 November 1988, see column 10, lines 22-39	1,2/12,14
X	US, A, 5,128,458 (MONTGOMERY ET AL.) 07 July 1992, see column 1, lines 48-67; column 17, line 51 through column 19, line 68.	3-11
X/Y	US, A, 4,861,759 (MITSUYA ET AL.) 29 August 1989, see column 2, line 45 through column 3, line 42.	14/1,2, 15-32
Y	US, A, 3,817,982 (VERHEYDEN ET AL.) 18 June 1974, see column 1, lines 40-45, column 3, lines 1-10	1,12,14
Y	US, A, 4,879,277 (MITSUYA ET AL.) 07 November 1989, see entire document.	15-32

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
22 AUGUST 1994

Date of mailing of the international search report
SEP 19 1994

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Authorized officer
JAMES O. WILSON
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/05790

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61K 31/70; C07H 19/00
US CL :514/46, 47, 49, 50; 536/4.1, 27.14, 28.2; 544/264
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/46, 47, 49, 50; 536/4.1, 27.14, 28.2; 544/264

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS ON LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X/Y	US, A, 4,788,181 (DRISCOLL ET AL.) 29 November 1988, see column 10, lines 22-39	1,2/12,14
X	US, A, 5,128,458 (MONTGOMERY ET AL.) 07 July 1992, see column 1, lines 48-67; column 17, line 51 through column 19, line 68.	3-11
X/Y	US, A, 4,861,759 (MITSUYA ET AL.) 29 August 1989, see column 2, line 45 through column 3, line 42.	14/1,2, 15-32
Y	US, A, 3,817,982 (VERHEYDEN ET AL.) 18 June 1974, see column 1, lines 40-45, column 3, lines 1-10	1,12,14
Y	US, A, 4,879,277 (MITSUYA ET AL.) 07 November 1989, see entire document.	15-32

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"A" document defining the general state of the art which is not considered to be of particular relevance

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